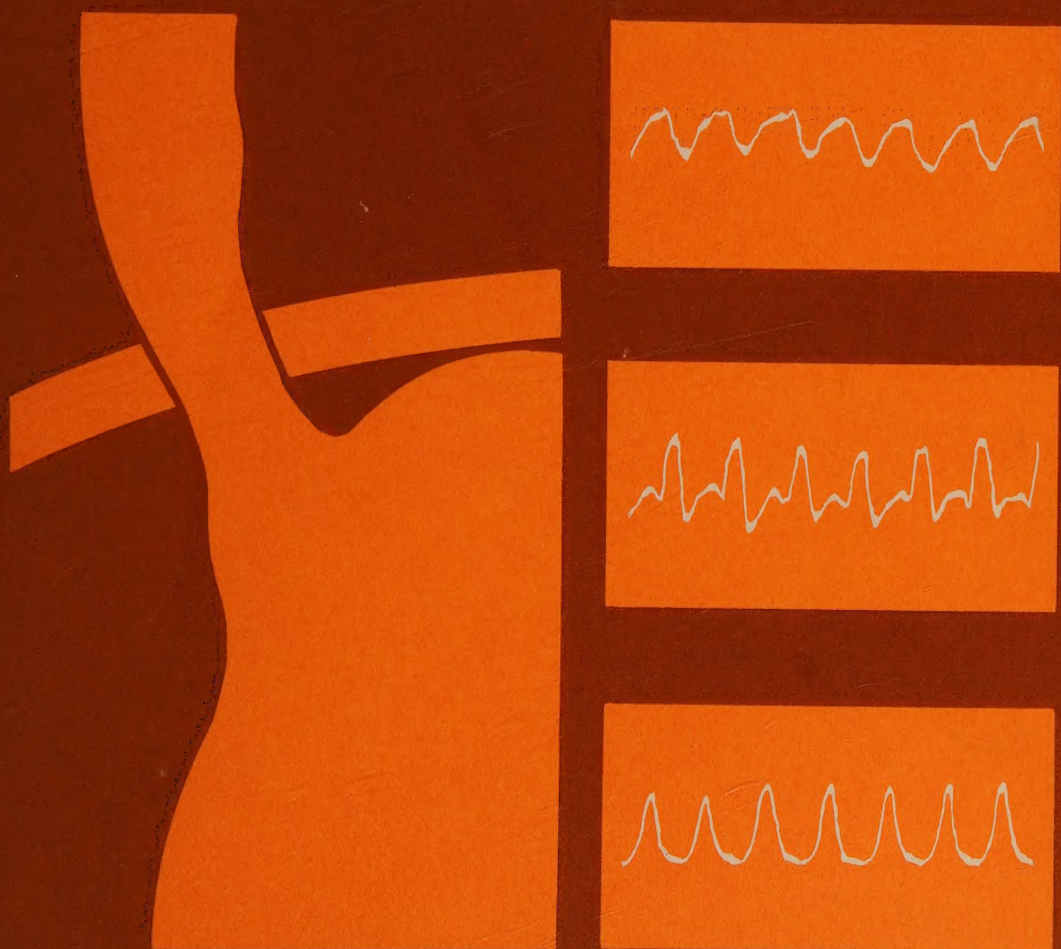


SVEND ARNE PEDERSEN

GASTROESOPHAGEAL SPHINCTER
PRESSURE IN DISEASES OF
THE STOMACH
DUODENUM AND BILIARY TRACT



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in Diseases of the Stomach,
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To Kirsten, Anne Kathrine and Jens Christian

Gastroesophageal Sphincter Pressure in Diseases of the Stomach, Duodenum and Biliary Tract

by

Svend Arne Pedersen

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Preface

The present work was carried out during my appointment as research fellow at the University of Odense, and the studies were done at the Department of Thoracic and Cardiovascular Surgery, Odense University Hospital. The head of the department, Professor H. Rahbek Sørensen, M.D., offered me extremely favorable working conditions, and followed the progress of my work with keen interest.

My teachers of gastroenterology, F. Truelsen, M.D. and C. M. Madsen, M.D., heads of the Department of Gastrointestinal Surgery, and Inger-L. Marner, M.D., head of the Department of Medical Gastroenterology, supported me in a variety of ways and also showed me the confidence to let me examine their patients.

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Odense University Hospital

January 1975

Svend Arne Pedersen

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CHAPTER I

Aim of the present study

The aim of the present study has been to investigate the relationship of gastroesophageal sphincter pressure to different neurogenic and hormonal factors relating to the stomach, duodenum and biliary tract. The choice fell on this subject because there was a reason to suppose that the results might contribute to a better understanding of the mechanisms regulating sphincter pressure. This supposition was based on the fact that sphincter pressure is not controlled only by direct nervous innervation but is also dependent on reflexes from the stomach and biliary tract, gastrointestinal hormones and the intragastric milieu.

With this purpose in view manometric studies were made of the characteristics of the gastroesophageal sphincter in normal subjects as well as in patients before and after operation for commonly occurring organic and non-organic disorders of the upper abdomen.

The subject was approached from a purely pathophysiological angle, and no comparison between the various diagnostic methods was intended.

CHAPTER II

Use of perfused catheters for recording of pressures in the gastroesophageal sphincter and the corpus of the esophagus

previous technical investigations

Pert, Davidson, Almy, and Sleisenger (1959) were the first to use an infused system for recording of pressures in the gastroesophageal sphincter and the corpus of the esophagus. They used a flow of water at the rate of 3.0 ml per hr, and their argument for using perfused catheters was that "the replacement by the pump of the small amounts of fluid being lost at the dependent tip of the catheters diminishes the possibility of damping in the pressure transmission because of air bubbles". They did not report sphincter pressure measurements. The first quantitative study was published by Cohen (1965). He studied normal subjects and patients with achalasia and found that with the perfused system, as opposed to the non-perfused, patients with achalasia had a hypertensive gastroesophageal sphincter.

A more well-founded argumentation for the use of flow is based on the results of two works from the mid-sixties (Harris and Pope, 1964; Harris, Winans, and Pope, 1966). These investigators made "pull-through" studies of the human anal sphincter using partly non-perfused, partly perfused catheters. Using non-perfused catheters they found that the pressure recorded from the anal sphincter was directly related to the last pressure to which the recording tip had been exposed before it entered the sphincter, and not an expression of sphincter contraction or force. By infusing small increments of fluid into the system it was possible to measure a physiologically significant pressure, the pressure required to break the sealing action of the sphincter.

These results laid the groundwork for the investigations into the technical problems that have been carried out in recent years. Two different and supplementary procedures were employed – *in-vitro* studies with the use of models, and experimental studies on humans and animals.

The model studies were introduced by Pope (1967). He designed a model of the gastroesophageal sphincter by means of an excised segment of human or canine esophagus. An inflatable cuff was wrapped around the midpoint of the segment, and the cuff pressure was continuously measured. Intraluminal pressure was studied using latex balloons and polyvinyl or polyethylene catheters with either a side or an end hole. The flow rate was 0.05 to 0.8 ml per min. When comparing intraluminal pressure with cuff

pressure it was found that neither catheter material nor type of recording tip made any difference in the values obtained. All the balloon-tipped catheters tended to overestimate cuff pressure, and there was moderate to marked variations in different balloons of the same size. The reading from uninfused open-tipped catheters showed much variation, tended to underestimate cuff pressure, and did not bear a linear relation to increase in cuff pressure. The infused catheters followed cuff pressure almost exactly, and displayed extremely little variation from catheter to catheter. From these results it was concluded that infusion of small quantities of fluid into the lumen of a closed sphincter allows more accurate prediction of sphincter force of closure than does static measurements of intra-sphincteric pressure.

In 1970 Pope reported the results of an *in-vitro* study of the importance of the slow rate by recording of rapid variations in pressure. He had designed a model by tying a segment of excised human esophagus between two tubes and suspended the test segment in a glass cylinder filled with water. Pressure in the cylinder was varied by raising or lowering the hydrostatic head of a connected bottle. The recording system was inserted through the tube into the interior of the test segment of esophagus. It was thus possible to compare pressures from the internal and external aspect of the test segment at the same time. It was found that with slow variations in the external pressure uninfused catheters underestimated pressure while infused catheters agreed exactly with the external pressure on the esophagus.

This model also demonstrated that rapidly changing pressure events could not be recorded accurately if the infusion rate was too low. It was concluded that the rate of infusion is crucial when estimating the rapidly changing pressure waves in the esophagus *III in-vivo*.

Dodds, Hogan, Reid, Stewart, Linehan, Stef, and Arndorfer (1972a), using the same model as Pope (1970), studied some variables affecting the reliability of manometric recordings. In the model they used test pressure complexes with variation in amplitude and duration, and in the recording system the infusion rate was varied from 0 to 12 ml per min. They found that pressure recording accuracy was inversely related to the pressure amplitude tested, directly related to duration of pressure complex, and directly related to infusion rate.

The latest reported model-study is by Waldeck, Jennewein, Siewert, and Nieder (1973). They used a model consisting of a piece of canine esophagus placed in a glass cylinder, and investigated the relationship of variations in external pressure to pressure recorded from the inside of the esophagus segment. It was demonstrated that pressures transmitted by non-perfused water-filled catheters were too low, while the values recorded by perfused catheters agreed exactly with the external pressures. They also investigated the rate of perfusion necessary when recording by means of a continuous withdrawal

procedure. A single catheter with four side holes of 1 mm and at the same level was used, and it was shown that the pressure transmissions depended upon the rate of perfusion, the speed of withdrawal, and the height of the artificially induced external pressure. It was found that with a model pressure of 100 mm Hg and a withdrawal speed of 5 mm per sec the perfusion rate had to be at least 5 ml per min. Conditions in the model similar to recordings of peristalsis in the corpus of the esophagus were created. With a peristaltic speed of 6 cm per sec and a maximum amplitude of 200 mm Hg the perfusion rate had to be 30 ml per min. Pressure transmission was also studied by means of different types of balloons. Latex balloons were very unreliable pressure transmitters, and it was demonstrated that the false transmission was due to deformation. Model experiments with polyester balloons yielded a pressure transmission of up to 250 mm Hg without deviation from the model pressure, and the balloons also yielded an exact transmission of rapid changes in pressure.

These model-studies have given indications of the criteria which a certain system must fulfil to be accepted as suitable for *in-vivo* recording of pressures. On examination of the gastroesophageal sphincter pressure the commonest procedure is a "pull-through" study with stepwise withdrawal of the pressure probe from the fundus through the sphincter and into the corpus of the esophagus. Perfused – but not non-perfused – catheters are suitable for this purpose. It is an example of slow variations in pressure, and the recording will be reliable irrespective of the flow rate. If, instead of stepwise, continuous withdrawal is used, the pressure variations will no longer be slow. The variation per time unit will depend on the gastroesophageal pressure gradient and the speed at which the probe is withdrawn; consequently the flow rate is of great importance with this procedure. Relaxation in the sphincter area on swallowing can also be recorded by perfused catheters irrespective of the flow rate but, the duration of relaxation will depend on the flow rate. The higher the flow rate the sooner the pressure will return to the basal value after relaxation, and therefore the latter will be recorded as being of shorter duration. By recordings from the corpus of the esophagus in relation to swallowing the rises in pressure will be sharp and of short duration, and here the flow rate will be of prime importance. Exact recording will have its limitation in that theoretically a system will only be able to record a rise in pressure which per time unit equals the rise obtained by total blocking of the distal opening of the catheter.

The conclusions from the model-studies have been verified *in-vivo*. Pope (1967) compared sphincter pressure recorded by non-perfused and perfused catheters in a study of 40 subjects with and without reflux. The perfusion rate was 0.05 to 0.8 ml per min. and the pressures were independent of the rate of flow. Pressures recorded by perfused catheters were higher than those

recorded by non-perfused catheters. Winans and Harris (1967) likewise made comparative studies of perfused and non-perfused systems. Their material consisted of healthy subjects and subjects with gastroesophageal reflux, and they used an infusion rate of 0.36 to 0.48 ml per min. Pressures recorded from the stomach and esophagus by infused and uninfused systems were the same, while the pressures measured in the gastroesophageal area were quite different. In all cases pressures recorded by the uninfused system were lower than those recorded by infused systems. Both investigations were carried out employing intermittent withdrawal technique. Rinaldo and Levey (1968) used continuous withdrawal and different flow rates in a study of the gastroesophageal sphincter in normal human subjects. The flow rates were 0.297, 1.14, and 2.24 ml per min, but the speed of withdrawal was not stated. Mean pressures were found to be equal, independent of flow rate. These results were obtained with the subjects in a state of held expiration. Waldeck *et al.* (1973) also tested the reliability of the continuous withdrawal method in humans and animals. The studies were made in a state of held expiration, and at a withdrawal-speed of 5 mm per sec. At this speed a perfusion rate of 2 ml per min proved sufficient for transmitting an accurate resting pressure profile.

These results have confirmed two of the conclusions arrived at in the model-studies, viz. that sphincter pressure is higher by perfused than by non-perfused catheters, and that the pressure is independent of flow rate. In this context it should be remembered that sphincter pressure is here defined using fundic pressure as reference. Increasing flow rates will be followed by rises in baseline-pressure, and if absolute values are wanted instead of gradients, the recorded values have to be reduced by a factor, which equals the pressure induced into the system by the flow.

The fact that infused systems record higher pressure values than non-infused is, of course, not tantamount to the higher values being "more correct". However, Cohen and Harris (1970) demonstrated that the values recorded by perfused catheters were directly correlated to a physiological parameter – sphincter strength. They made comparative studies of sphincter strength and sphincter pressure. Sphincter strength was defined as the force in grammes required to pull a 12 mm Teflon ball from the stomach through the sphincter and into the esophagus. These two parameters were measured in humans by means of a single probe, consisting of the Teflon ball and two catheters with side holes. Comparison of strength in grammes and pressure in mm Hg showed excellent correlation for both spontaneous and induced changes in strength. The results demonstrated that gastroesophageal sphincter pressure measured by a continuous infusion of fluid is an accurate index of sphincter strength.

The third conclusion of the *in-vitro* studies – that a reliable recording of

rapid variations in pressure requires a high flow rate – has been confirmed repeatedly *in-vivo*. Dodds *et al.* (1972a) recorded the pressure variations induced by swallowing in the corpus of the esophagus of healthy human subjects. The recorded pressure plateaued at an infusion rate of 1.6 to 3.2 ml per min in the distal four-fifths of the esophagus. In the proximal part, the recorded pressure kept increasing as the infusion rate was increased to 12 ml per min. Hollis and Castell (1972) also recorded esophageal peristalsis in healthy human subjects and used ten different infusion rates from 1 to 23 ml per min. They obtained a hyperbolic pressure response curve to increasing infusion rate, indicating that increased amplitude of esophageal peristalsis was obtained by increasing the infusion rate until a rate was reached which resulted in near-maximum pressure. Linear transformation of this curve, using a reciprocal plot, allowed calculation of the maximum amplitude. The calculated maximum response ranged from 54 to 254 mm Hg. The actual recording of these high values would necessitate a very high flow rate, but the authors also demonstrated that the use of four different infusion rates in the range of 1.61 to 12.1 ml per min was sufficient for a reliable determination of the calculated maximum amplitude. Waldeck *et al.* (1973) found in animal experiments that a perfusion rate of about 30 ml per min was necessary for reliable recording of esophageal peristalsis. However, this rather high perfusion rate elicited secondary peristalsis which disturbed the pressure measurements.

As regards the basal technical problems associated with recordings of those pressure variations that are elicited on swallowing, the results of the *in-vitro* and the *in-vivo* studies are well in keeping. Recording of the actual pressure variations will require very high flow rates, and the most expedient procedure will therefore be to use calculated maximum response, and to calculate this parameter from different and more moderate flow rates.

The use of perfused catheters in experimental and clinical studies have brought to light problems which could not be predicted in the model-studies. The problems arose in connection with the construction of a pressure probe consisting of several separate catheters. Kaye and Showalter (1971) studied the manometric characteristics of the sphincter in healthy subjects. They used three continuously perfused recording catheters, the side holes of which were at an identical level and equidistant around the circumference of a circle. With each type of tracing there were differences between the three leads with respect to the various characteristics, including the maximum sphincter pressure. Similar results were later reported by Winans (1972) and Zabinski, Biancani, Philips, and Spiro (1972). They demonstrated that the spatial orientation of the recording hole had an effect upon the type of tracing obtained, and suggested that this difference was due to anatomical features. Another problem was related to the total diameter of the pressure

probe. Normally the sphincter is a closed area, and pressure recording will necessarily cause a distension with subsequent increase in tension in the circular muscle fibres. In consequence, it could be expected that pressure probes with different diameters would record different pressures. Biancani, Spiro, and Bejar (1973) demonstrated that this is so. They made comparative studies of sphincter pressures recorded by probes with a diameter of 2.5, 5.0, 7.5 and 10 mm, respectively. The studies were made on human subjects with competent sphincter, and the investigators found a clear relationship of mean sphincter pressure to the diameter of the probe. The pressure was high when using the smallest diameter, decreased at intermediate diameters and increased again when the biggest diameter was used.

In this review of perfused catheter systems it should also be mentioned that research of recent years has produced other recording systems. In addition to the *in-vitro* studies mentioned in the foregoing, Waldeck *et al.* (1973) made *in-vivo* studies with polyester balloons. They found that with this type of balloon a reliable recording was obtained of both the basal sphincter pressures and the pressure changes which are elicited in the corpus of the esophagus on swallowing. A few workers have had occasion to try the new subminiature strain gauges *in situ* (Millhon, Hoffman, and Jarvis, 1968; Dodds *et al.* 1972a; Waldeck *et al.* 1973). It is argued that the diameter is too big, that they are difficult to maintain, and that they are sensitive to changes in temperature. On the other hand, it is generally agreed that with minor technical modifications they will prove suitable for recording of pressures in the sphincter and the corpus of the esophagus.

This review illustrates the rapid progress that have been made in this field in recent years, and the various centres are continuously working intensively at improving the methods. Today, however, the choice lies between polyester balloons, subminiature transducers *in situ*, and perfused catheters.

Polyester balloons have appeared within the last year; the preliminary results are good but these balloons are not yet generally available on the market.

Subminiature transducers *in situ* are still on the experimental stage and have not yet reached a sufficiently high technical standard.

Finally, there are perfused catheters, which method has been used in the present study. The primary aim has been to investigate the gastroesophageal sphincter pressure, and for this purpose a low flow rate is of importance; first, because this will not elicit any disturbing secondary peristaltic activity, second, because at a low rate it will be possible to record pressures over a longer period without inducing alterations in the milieu of the stomach – the last is of prime importance since the pH of the gastric secretion is essential to the regulation of the sphincter pressure.

CHAPTER III

Previous investigations on neurogenic and hormonal receptors in the gastroesophageal sphincter

To be able to draw conclusions from the results obtained by manometric studies of the gastroesophageal sphincter pressure it is necessary to have a thorough knowledge of the basal mechanisms involved in the normal physiological control of the sphincter pressure. Scientific achievements of late have enlarged our knowledge in this respect, and it has now been proved that both neurogenic and hormonal factors play a decisive role.

The first systematic studies on neurogenic receptors in the gastroesophageal sphincter date from the end of the fifties and the beginning of the sixties (Trounce, Deuchar, Kauntze, and Thomas, 1957; Ellis, Kauntze, Nightingale, and Trounce, 1960a; Ellis Kauntze, and Trounce, 1960b; Adams, Brian, Ellis, Kauntze, and Trounce, 1961; Clark and Vane, 1961; Schenk and Frederickson, 1961). The results were mutually contradictory, and on the evidence of the latest technological and pharmacological advances these early studies must today be regarded as inconclusive.

Bailey (1965) was the first to use the newer pharmacological drugs, and he demonstrated that circular smooth muscle from the sphincter area of the guinea pig contains three neurogenic receptor types. Acetylcholine induced contraction. The sympathomimetic amines norepinephrine, epinephrine, and isoprenaline all produced relaxation. Pronethalol antagonised the relaxation, and in some experiments reversed the epinephrine response to a small contraction. Dihydroergotamine antagonised the contraction produced by epinephrine in the presence of pronethalol. These results provided evidence of the presence of two groups of adrenergic receptors in guinea pig – alpha excitatory and beta inhibitory receptors. Three years later the existence of the same types of receptor, with the same types of response to stimulation, was demonstrated in circular smooth muscle from the sphincter area in the cat (Christensen and Daniel, 1968). Misiewicz, Waller, Anthony, and Gummer (1969) were the first to demonstrate that circular smooth muscle from the sphincter area in man has the same receptor types as muscle from the guinea pig and the cat. They found that acetylcholine elicited contraction, and that norepinephrine produced contraction or relaxation. The contractions were blocked by phentolamine, and the relaxation prevented by beta-blocking. The muscles were always relaxed by isoprenaline and this ef-

fect was prevented by pronethalol. These findings demonstrated that cholinergic and alpha-adrenergic activity contracts human circular sphincter muscle whilst beta-adrenergic activity produces relaxation.

Later studies have mainly focussed on comparing the pharmacological characteristics of the sphincter musculature with those of musculature from adjacent areas. The studies have been made on muscle strips from the opossum, an animal often used as model for the human esophagus. Christensen (1970) investigated the characteristics of muscle from the sphincter segment and more rostral levels of the esophagus. Acetylcholine, carbachol, and metacholine all caused contractions, which were qualitatively similar at all levels. Norepinephrine, both alone and with propranolol, caused contraction but both threshold concentrations and maximum responses were very different among levels. Higher levels of the esophagus had larger threshold concentrations and lesser maximum response than lower levels. This greater difference in sensitivity to norepinephrine than to the other agents made the author suggest that the adrenergic innervation is important in defining the lower esophageal sphincter. Lipshutz and Cohen (1971) studied musculature from the sphincter area, antrum, and corpus of the esophagus. With regard to length-tension characteristics, they found that muscle from the sphincter developed a greater peak active tension, and required less stretch to reach its optimal length. The reaction to acetylcholine was a contraction. Compared to muscle from the other regions, muscle from the sphincter area developed greater tension and responded at a lower threshold dose. Norepinephrine contracted all esophageal strips, and again the muscle from the sphincter area developed a greater maximum active tension and responded at a lower threshold dose. The authors concluded that muscle from the sphincter area has physiological characteristics that are different from those of muscle from the adjacent esophagus and stomach. It has different length-active tension properties, it responds at lower threshold to naturally occurring neural agonists, and at its length of optimal tension it develops a greater active tension to each agonist than the adjacent region. The lower threshold was most marked for norepinephrine, and it is suggested that the latter is a major determinant of sphincter function *in-vivo*.

These *in-vivo* experiments demonstrated that the sphincter is a well-defined structure, defined on the basis of quantitative pharmacological characteristics. In several respects this knowledge is consistent with the findings of manometric studies of sphincter pressure in relation to injection of drugs acting on the autonomic nervous system.

Bettarello, Tuttle, and Grossman (1960) investigated the effect of atropine sulphate and bethanechol chloride on resting sphincter pressure in man. Intravenous administration of 1.2 mg atropine was followed by a significant reduction in mean pressure. Subcutaneous administration of 5 mg

bethanechol resulted in a significant increase in mean pressure. Van Der-stappen and Texter (1964) studied the effect of intravenous injection of 30 mg propantheline on resting sphincter pressure. They observed a significant decline in mean sphincter pressure. Lind, Crispin, and McIver (1968) studied the reaction to atropine in normal human subjects. Subcutaneous injection of atropine, 0.025 mg per kg, caused a significant fall in mean sphincter pressure. All these studies were made with non-perfused catheters, but later studies with perfused catheters have confirmed the findings. Using the latter technique Hookman and Fleischer (1969) studied the reaction of human sphincter to prostigmin. Subcutaneous injection of 0.015 mg per kg induced an increase in sphincter pressure from a mean of 20 to 30 mm Hg. Cohen and Lipshutz (1970) investigated the effect of atropine sulphate on human resting sphincter pressure. Intravenous injection of atropine in a dose range of 0.01 to 0.02 mg per kg was followed by a significant decline in pressure from a mean of 22 to 9 mm Hg. Pedersen, Nielsen, and Sørensen (1971) demonstrated that intramuscular injection of a combination of atropine sulphate, 0.01 mg per kg, and hexamethonium bromide, 1 mg per kg, induced a significant decrease in mean sphincter pressure. A single human study, using drugs with effect on alpha and beta-adrenergic receptors, has been reported (Zfass, Prince, Allen, and Farrer, 1970). Intravenous infusion of isoproterenol, $0.03\mu\text{g/kg}$ per min for 5 min, induced a significant reduction in mean sphincter pressure. Intravenous infusion of the beta-blocking agent Alprenolol® was followed by a significant increase in pressure. No changes were observed after infusion of phenylephrine (an alpha-adrenergic stimulating drug) or phentolamine (an alpha-adrenergic blocking agent Alprenolol® was followed by a significant increase in in accordance with the findings of *in-vitro* investigations. The author attributes the failing response to alpha stimulating and alpha blocking drugs to the dosage being too low. This is a likely explanation, particularly in the light of the later report by Goyal and Rattan (1973), who demonstrated that injection of adrenergic stimulating and blocking drugs in opossum was followed by changes in sphincter pressure; these findings were in agreement with those of the *in-vitro* investigations. Intravenous injection of phentolamine, 1 mg per kg, caused a fall in sphincter pressure and antagonised the stimulating action of norepinephrine. Injection of propranolol, 1 mg per kg, increased sphincter pressure and antagonised the depressive action of isoproterenol.

When comparing the knowledge gained by *in-vitro* studies with the findings of manometric studies it should be born in mind, however, that stimulation or inhibition by injection of drugs are unphysiological events. Normal physiological activity is conditioned by a local release of transmitter substance, and not by universal augmentation of the blood concentrations. Fur-

thermore, injection of drugs with action on the autonomic nervous system will elicit varying activity in all organs containing receptors that respond to the agents concerned. It is, therefore, possible that secondary effects on sphincter pressure are elicited, partly via neurogenic reflex pathways partly via a shift in the blood concentrations of gastrointestinal hormones.

Hormonal regulation of the gastroesophageal sphincter has been the subject of many studies in recent years, and the findings have contributed considerably to a better understanding of the physiological and pathophysiological reactions of the sphincter. Bennet, Misiewicz, and Waller (1967) were the first to demonstrate the effect of gastrin on circular muscle from the human sphincter. Nine muscle strips were investigated. Gastrin caused contraction of four out of six strips, and one of the remaining three strips contracted to pentagastrin. Three later reports, all using circular sphincter muscle from opossum, have confirmed this result, and at the same time elucidated the mode of action. Lipshutz and Cohen (1971) found that increasing concentrations of gastrin I in the perfusion fluid were accompanied by increasing contraction. The reaction to doses of gastrin beyond the dose that gave the peak response, was a marked diminution in response. The effect has been compared with that on muscle from the antrum and the corpus of the esophagus. The threshold for sphincter muscle occurred at a lower gastrin I dose, and it developed a greater active tension at lower gastrin I doses than muscle from the adjacent regions. In the investigations by Lipshutz, Tuch, and Cohen (1971) the site of action was determined by utilizing a series of chemicals that selectively antagonise one step that may be required for the action of gastrin I. It was concluded that the response to gastrin I is transmitted through cholinergic nerves. The mode of action was found to be a stimulation of postganglionic cholinergic nerves to release acetylcholine. Lipshutz, Hughes, and Cohen (1972) adduced further evidence of the existence of this mechanism. They found that the reaction to acetylcholine remained unchanged following gastrin antiserum, but that the reaction to gastrin I was markedly inhibited. In brief, these *in-vitro* studies have demonstrated that gastrin contracts circular muscle strips from the sphincter area, and that the effect is exerted via a gastrin-conditioned liberation of acetylcholine. Furthermore, they have shown that, quantitatively, sphincter muscle reacts in another way than muscle from the adjacent regions.

Animal experiments and human studies of late have shown that this *in-vitro* effect of gastrin is also demonstrable in *in-vivo* studies of sphincter pressure. Giles, Mason, Humphries, and Clark (1969a) were the first to point out that exogenous gastrin raises resting sphincter pressure. They used non-perfused catheters, and the effect can therefore not be quantified. Subsequent studies made with perfused catheters partly on opossum, partly on human subjects have confirmed, however, that gastrin raises sphincter pressure. Lip-

shutz and Cohen (1971) constructed dose-response curves for the effect of intravenous injection of gastrin I on sphincter pressure in opossum. The response occurred within 1 min from the beginning of the injection, peaked at three, and terminated within ten minutes. The maximum response, an increase in pressure of 290 per cent, was obtained at a dose of 1.0 μg per kg. Doses beyond 1.0 μg per kg gave a response less than maximum.

The first investigations on humans, with perfused catheters, were carried out by Castell and Harris (1970). They studied the effect of subcutaneous injection of 1.0 μg per kg of pentagastrin. The result was an increase in mean sphincter pressure. Sphincter pressure began to rise within 2 min from the start of the injection, reached a peak by 7 min, and had returned to pre-injection level by 30 min. In the subsequent years three works were published, which all defined the dose-response relationship of subcutaneous pentagastrin to sphincter pressure (Levine and Castell, 1970; Rosenberg and Harris, 1971; Hollis, Levine, and Castell, 1972). A representative dose range of pentagastrin was used in all cases and it was a common feature of the results that pentagastrin increased sphincter pressure, that the effect was recordable within few min, and reached maximum after 8 to 10 min. Levine and Castell (1970) found the threshold value to be 0.6 to 1.0 μg per kg. The mean maximum increase was 13.0 mm Hg at a dose of 4.0 μg per kg, and this increase was significantly greater than the increase after 6.0 μg per kg. Rosenberg and Harris (1971) found a peak sphincter rise of 270 per cent at a pentagastrin dose of 0.5 μg per kg. At higher doses responses decreased progressively to a plateau of 100 per cent increase in pressure above 1.5 μg per kg. Hollis *et al.* (1972) defined the threshold to be 0.6 μg per kg, and the maximum change in sphincter pressure occurred at a dose of 2.0 to 4.0 μg per kg. The mean increase in pressure after this dose of pentagastrin was significantly greater than the response obtained after 6.0 μg per kg.

There are three reports on the reaction to intravenous injection of pentagastrin. Nebel and Castell (1972) constructed a dose-response curve for the sphincter response to rapid intravenous injection. The curve was sigmoid in shape with a peak change in pressure of 38.0 mm Hg at a pentagastrin dose of 0.6 μg per kg. Jennewein, Waldeck, Siewert, and Weiser (1973) found a peak sphincter response of the same magnitude with a pentagastrin dose of 0.3 to 1.0 μg per kg. Frank, Walker and Fordtran (1973) investigated the reaction to continuous intravenous infusion of pentagastrin in normal human subjects. They used two different doses, 0.015 and 0.025 $\mu\text{g/kg}$ per min, respectively, and gastric acid was constantly removed during the study. The lower dose resulted in an increase in mean pressure from 19 to 24 mm Hg. The higher dose was followed by an increase from 21 to 29 mm Hg. After 1 hr of continuous infusion, an intravenous bolus of 0.5 μg per kg of pen-

tagastrin was injected. In both series the reaction was an increase in sphincter pressure to 39 and 45 mm Hg, respectively.

The response to intravenous injection of gastrin I was studied by Cohen and Lipshutz (1971). The resulting increase in pressure was expressed in percentages of the initial resting pressure. On injection the pressure rose promptly, peaked at 3 min, and returned to normal within 10 min. The threshold dose was 0.025 μ g per kg, and the maximum response of a 460 per cent increase in resting pressure was attained at a dose of 0.7 μ g per kg.

The results of these studies are unambiguous. Exogenous gastrin increases resting sphincter pressure, and the effect may be produced by a dose smaller than that necessary for eliciting maximum acid secretion. In relation to these results several workers have investigated whether the effect can be reproduced by procedures which inhibit or excite the release of endogenous gastrin. Castell and Harris (1970) studied the effect of changes in the milieu of the stomach on resting sphincter pressure. Hydrogen ion activity of the gastric contents was altered by instillation of either 0.1 n hydrochloric acid or 0.1 n sodium hydroxide. Prompt changes in pressure were noted with the alternate instillation of acid and alkali. Sphincter pressure decreased consistently when acid was instilled and, conversely, increased when alkali was placed in the stomach. When gastric hydrogen ion concentration was raised approximately 100 m-equiv per l, pressure decreased by a mean of 12.8 mm Hg. The mean increase in pressure on instillation of alkali was 19.6 mm Hg. Castell and Levine (1971) also evaluated the effect of changes in intragastric pH on sphincter pressure. Installation of 0.1 n hydrochloric acid resulted in consistent decreases in pressure. The subsequent installation of 0.1 n sodium bicarbonate resulted in striking increases in sphincter pressure to values much higher than basal levels. Cohen and Lipshutz (1971) used the same technique and an infusion rate of hydrochloric acid which was sufficient to keep a constant pH of 1.5. The result was a significant fall in mean sphincter pressure. Cohen, Lipshutz, and Hughes (1971) noted that infusion of acid elicited a significant fall in mean sphincter pressure from 19.4 to 6.1 mm Hg, equalling a reduction of 68.4 per cent.

These studies demonstrate an interrelationship between acidity of gastric contents and sphincter pressure. Procedures increasing acidity reduce pressure, and those reducing acidity increase sphincter pressure. Simultaneous recording of gastric acidity, serum gastrin, and sphincter pressure has not yet been reported, and it is therefore not possible to conclude that alterations in sphincter pressure are directly correlated to the alterations in serum gastrin. However, the investigations carried out by Lipshutz *et al.* (1972) lend support to this view. They studied sphincter pressure in relation to artificially induced changes in acidity of the gastric contents, with and without simul-

taneous injection of gastrin antiserum. The studies were made on opossum, and acidification of the stomach with 5 m-equiv of 0.1 n hydrochloric acid resulted in a prompt fall in pressure with a peak of 73 per cent. On installation of 5 m-equiv of 0.1 n sodium hydroxide the pressure increased. Administration of gastrin antiserum reduced this pressure increase from a mean of 38.7 to 3.0 mm Hg.

Consequently, it may be concluded that gastrin is a factor playing a decisive part in the normal control of sphincter pressure, and the two principal demands to be made in order for the effect to be accepted as physiological have been satisfied. Gastrin is active in doses smaller than those necessary to obtain maximum effect on the main organ (the oxyntic cells), and the effect can be reproduced by endogenous release. Therefore it was to expect that fasting serum gastrin would contribute considerably to the maintenance of resting sphincter pressure. This assumption was supported by studies which demonstrated a fall in pressure on intragastric acidification but, the conclusive proof was furnished by Lipshutz *et al.* (1972). They investigated the effect of gastrin antiserum upon resting sphincter pressure in opossum. Increasing amounts of antisera produced a graded inhibition in pressure, and the maximum inhibition represented a 80 per cent reduction. This inhibition was similar to the reduction obtained on suppression of endogenous release by exogenous gastric acidification with hydrochloric acid.

The other gastrointestinal hormones have not been the subject of so many studies as gastrin, but there are a few reports on the effect of secretin, cholecystkinin and glucagon. Cohen and Lipshutz (1971) studied the effect of secretin. A secretin dose-response curve, beginning at the level of resting unstimulated sphincter pressure, showed no significant change with secretin in doses of up to 1 U per kg. During intravenous infusion of secretin, 0.65 U/kg per hr, the gastrin dose-response curve was shifted to the right but remained parallel to the original curve. The peak response to gastrin I was still attainable, but higher doses were required. Duodenal acidification with 0.1 n hydrochloric acid at 18 m-equiv per 15 min, was not followed by a significant decrease in sphincter pressure. The same procedure, performed on gastrin I stimulated sphincter, reduced pressure to normal. Jennewein *et al.* (1973) reproduced these effects of exogenous secretin in dogs. Infusion of 2 U/kg per hr had no effect on resting sphincter pressure but caused a shift of the dose-response curve for pentagastrin to the right. These results demonstrated that exogenous secretin in physiological doses is without effect on resting sphincter pressure, and that endogenous secretin does not produce changes in pressure. Secretin inhibits the gastrin-stimulated sphincter through competitive kinetics, and this effect satisfies the demands for a physiological activity. The effect is recordable after a dose smaller than that required to achieve maximum effect on the main organ (the exocrine

pancreas), and it is reproducible by procedures that promote the release of endogenous secretin.

Resin, Stern, Sturdevant and Isenberg (1972) have investigated the effect of intravenous injection of the synthetic C-terminal octapeptide of cholecystokinin on the normal human sphincter. The lowest dose used was 2.5 ng per kg, with a stepwise increase in dose every 10 min. The result was a significant fall in mean sphincter pressure. A dose of 20 ng per kg reduced mean sphincter pressure from 14.9 to 10.9 mm Hg. This dose equals the lowest one exerting maximum effect on bile emptying from the human gallbladder (Sturdevant, Stern, Resin, and Isenberg, 1972). However, the outcome of this study cannot be taken as a proof that cholecystokinin is involved in the normal physiological regulation of sphincter pressure. Stepwise increase in dose with a short interval between injections was used. Jennewein *et al.* (1973) investigated the dose-response relationship of a single intravenous injection of cholecystokinin to sphincter pressure in dogs. A dose of three Ivy dog U per kg reduced sphincter pressure, whilst a higher dose led to an increase. The same studies were made with caerulein. Like with cholecystokinin, lower doses relaxed the sphincter and higher doses increased pressure. Injection of caerulein was also investigated in man. Intravenous injection of 20 ng per kg caused a slight reduction in pressure. On the evidence of the investigations carried out by Bertaccini, Brabanti, and Franco (1969) the effect of caerulein may be accepted as being pharmacological and not physiological. These authors compared the effect of a fatty meal with that of an intravenous injection of caerulein on the gallbladder shadow after oral cholecystography in man. The effect of a fatty meal was equal to the effect observed with a dose of caerulein of 2.5 to 5.0 ng per kg.

The effect of glucagon on resting sphincter pressure in the dog was investigated by Jennewein *et al.* (1973). A single intravenous injection of 100 μ g per kg practically eliminated sphincter pressure. The dose-response curve to glucagon showed a dose-dependent decrease of pressure to doses ranging from 3 to 100 μ g per kg. Infusion of glucagon in a dose of 0.5 mg/kg per hr changed the dose-response curve to pentagastrin. The effect was a diminishing of the maximum response to pentagastrin, without a lateral shift of the dose-response curve. On increasing the glucagon dose to 1.0 mg/kg per hr, the pentagastrin effect on the sphincter completely disappeared. The effect of a single intravenous injection of 60 μ g per kg of glucagon on human resting sphincter pressure was also investigated. The results was a significant fall in mean sphincter pressure. The dose range of exogenous glucagon, which induces a physiological increase in serum glucagon is not known, but 60 μ g per kg are likely to be a pharmacological dose. Therefore it remains obscure whether glucagon is involved in the normal physiological regulation of sphincter pressure.

The aforementioned studies have demonstrated that the normal control of the gastroesophageal sphincter pressure is exerted via several, separately well-defined, neurogenic and hormonal factors. This cognition has been arrived at in a surprisingly short time – in the last three to four years – and this tells something about the intensity with which the subject has been studied. In the past time many ill-founded theories have been advanced about the mechanism involved in the control of sphincter pressure. These theoretical speculations have now been superseded by well-documented facts that form the basis of future research, and the clinical use of the manometric investigation.

Apparatus, methods and materials

Apparatus used for manometric investigation

The manometric studies were carried out by means of waterfilled polyethylene catheters (Clay Adams, PE 100, i. d. 0.8 mm, o. d. 1.5 mm). Each catheter had a side-hole, the smallest diameter of which equalled the internal diameter of the catheter. Distally to the side-hole the lumen was closed by a metal pin, and proximally the catheter was connected to a transducer (Elema-Schönander, EMT 35). The pressure probe consisted of three catheters with an equidistance of 5 cm between the side-holes. Distally the catheters were fixed in a short metal cylinder and, to ensure that the side-holes were free, the catheters were assembled by a mersilene thread distally to the middle side-hole. Each catheter was perfused by a continuous infusion pump (Braun-Melsungen, Unita I). The initial studies were carried out at a flow rate of 0.1 ml per min, but this was later amended to 0.15 ml per min.

Fig. 1 shows a diagram of the transducer with cock-system and catheter. The three-way stop-cocks stand in the position that were used during recording of the pressure curves. The top cock was used at calibration, and the cock to the left came into use if it was desired to flush out the system without breaking the continuity. A pressure interval of 20 mm Hg equalled 2 cm on the graph paper.

Fig. 2 pictures the pressure probe.

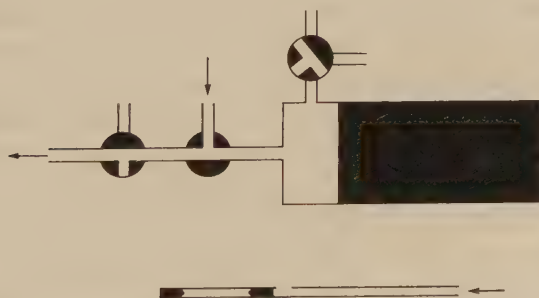


Fig. IV-1 Diagram of transducer with cock-system and catheter. The arrows indicate the passage of the fluid from the infusion pump via cock-system and into the catheter.

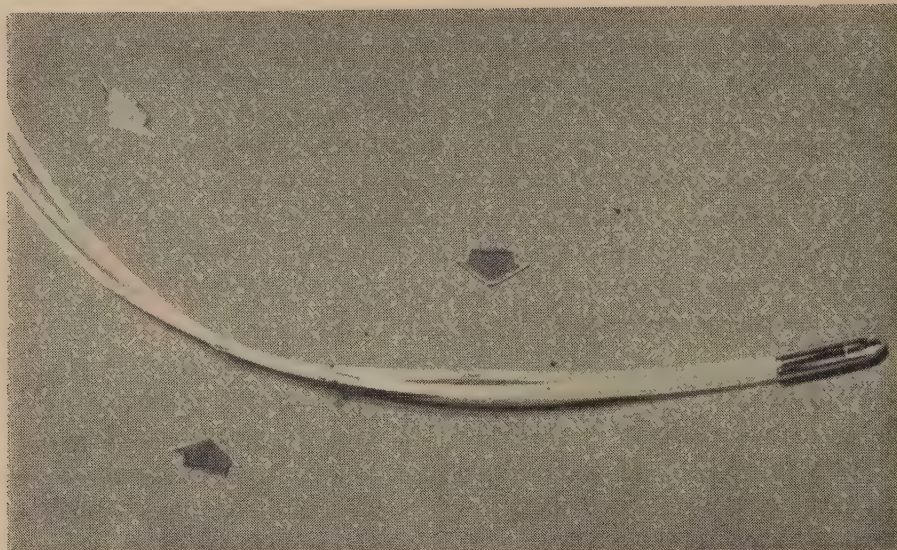


Fig. IV-2. Pressure probe. The diameter of the metal cylinder is 5 mm, and that of the assembled catheters 3 mm. Each side-hole is marked by an arrow.

Fig. 3 shows the apparatus used for withdrawal of the pressure probe. The horizontal lever is movable and can be fixed in the position wanted. At one end there is a binding screw, in which to fasten the probe. At the other end the lever is connected to a screw system which can be moved along the vertical lever. By means of this system the probe is pulled upwards, and a marking is made on the graph paper at every half cm.

Fig. 4 shows the components of the setup.

Method of manometric investigation

It is essential that the patient is informed in detail of the aim and procedures before the study starts. Not only out of regard for the patient but also because a technically satisfactory recording depends on a close cooperation between patient and investigator. The apparatus is very sensitive, and it is therefore necessary that the patient lies quite still on the couch. Moreover, in certain situations it is expedient to avoid the variations in pressure that are elicited on swallowing, and a protracted recording without the patient swallowing is only possible if he is unaffected by the procedure.

The pressure probe is introduced transnasally with the patient in the sitting position, and after a slight anesthesia of the nasal mucosa and pharynx with lidocaine (Xylocaine®). Due to the special construction of the probe

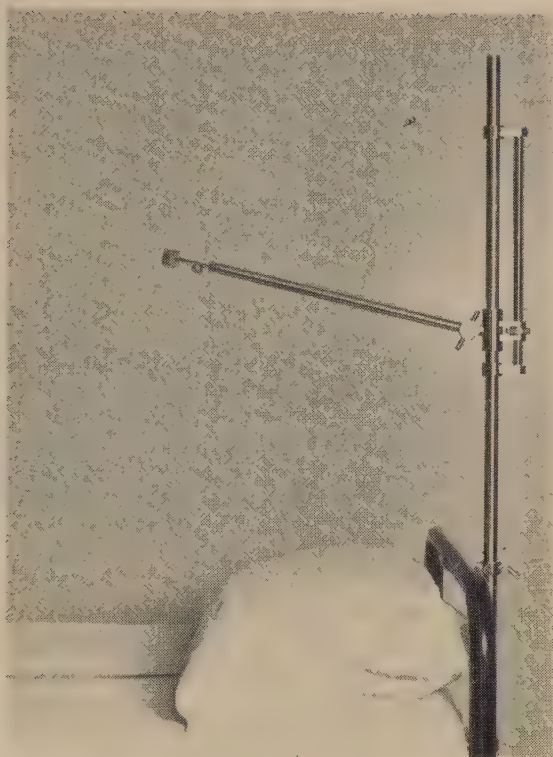


Fig. IV-3. Device used for withdrawal of the pressure probe. For further explanation see text.

the introduction does not cause the patient much discomfort. The metal cylinder is placed in the pharynx, and on the subsequent swallowing the cylinder with catheters pass into the esophagus. The patient is now placed in the supine position and the probe manually positioned in such a way that the lowest or the two lowest side-holes are sited in the stomach. To be able to register whether the pressure variations in the sphincter are due to swallowing, at least one side-hole must be sited in the corpus of the esophagus. After the probe has been maneuvered into the wanted position, it is fixed as previously described, and the withdrawal begins. By this procedure the pressures in stomach, gastroesophageal sphincter and corpus of the esophagus are recorded. The procedure takes about three quarters of an hr.

Characteristics and reading of curves

In a recording from the normal gastroesophageal region it is possible, on the basis of respiratory deflections and expiratory pressure, to define five

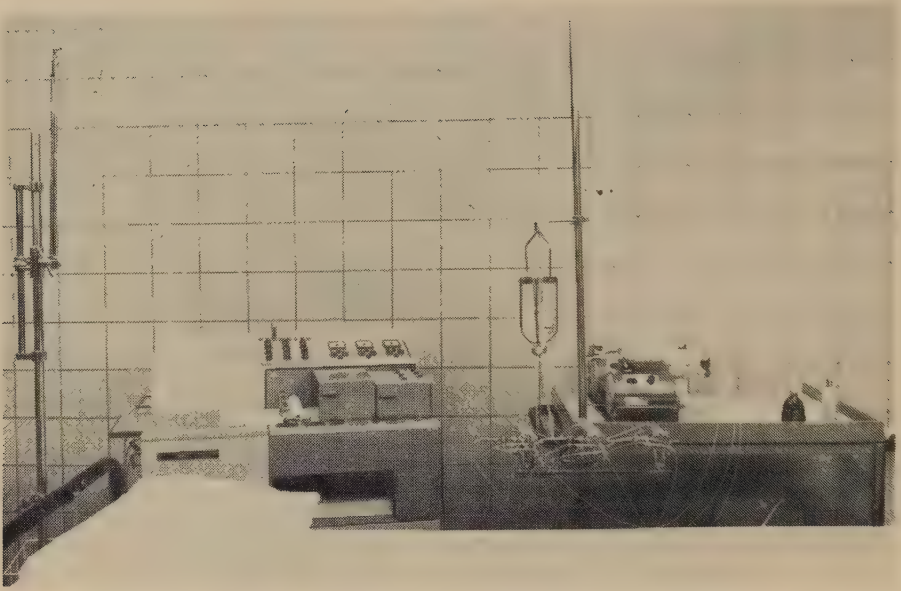


Fig. IV-4. Setup of the components. In the background the mingograph (Elema-Schönander, 81), in front the couch with the device for fixing and withdrawing the pressure probe; to the right the transducers and the infusion pump. The transducers are positioned 10 cm above the couch.

different segments (Fig. 5). At the bottom a typical curve from the stomach showing small respiratory deflections and increasing pressure on inspiration. At the top a curve from the corpus of the esophagus showing a fall in pressure on inspiration. Between these segments the gastroesophageal sphincter, characterized by a higher expiratory pressure than in the stomach. The spincter is tripartite. At the bottom an area with abdominal respiratory deflections. Next an area where the deflections in pressure are reversing from abdominal to thoracic type – the so-called respiratory reversal – and at the top an area with thoracic respiratory deflections.

A pressure recording will consist of these elements, and fig. 6 gives an example of an intact tracing. This tracing was made using the “pull-through” technique – intermittent withdrawal without swallowing. The procedure followed when reading the curves is outlined in the figure. Reading is made at the end of expiration, and the result is stated in mm Hg. By sphincter pressure is understood end-expiratory spincter pressure (A) less the expiratory pressure in the stomach (B).

Fig. 7 is an example of a tracing recorded with another technique – intermittent withdrawal with swallowing on each level.

The tracings mentioned are examples of the commonest type of tracing.

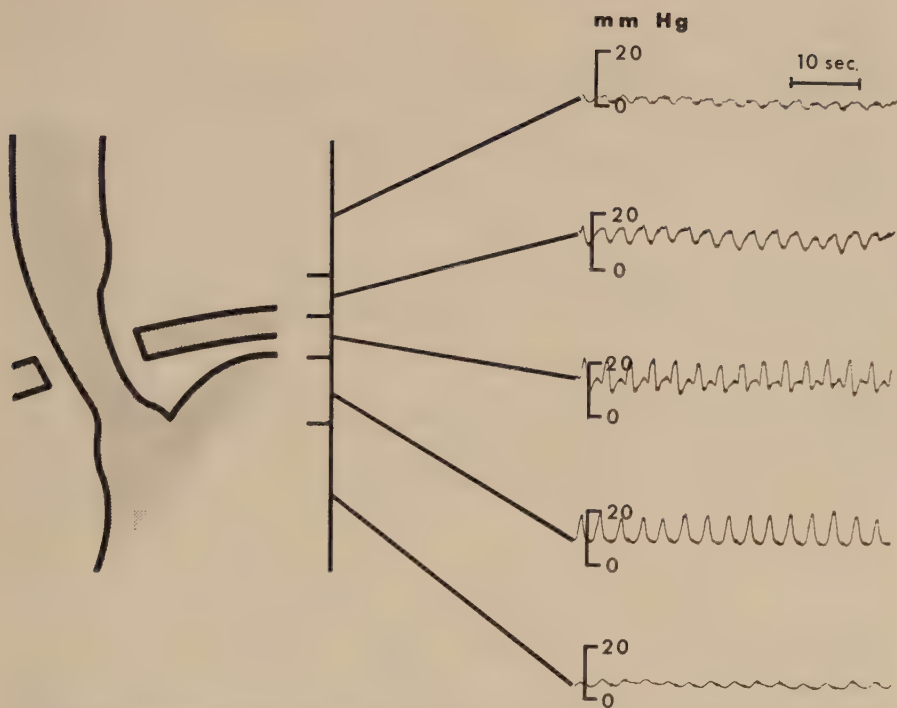


Fig. IV-5. Diagram of the esophagus and the types of curve which are characteristic of the various segments of the gastroesophageal region.

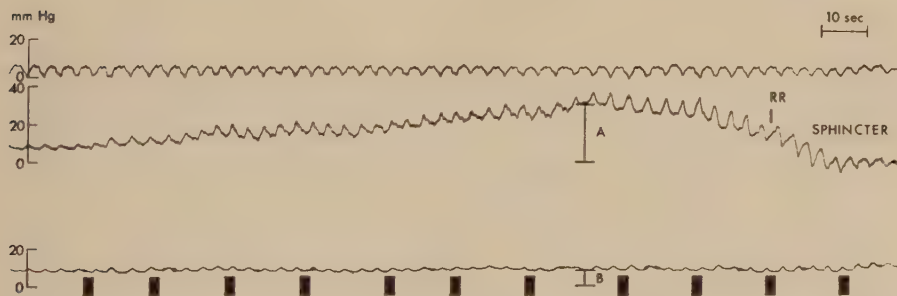


Fig. IV-6. Tracing made with "pull-through" technique. In this as well as in the following figures RR indicates the respiratory reversal, and each half cm of withdrawal is marked by a vertical bar.

It is characterized in that maximum pressure is a plateau with a constant pressure, in that there is only one segment with respiratory reversal, and in that swallowing elicits a decline in sphincter pressure to close to the fundic pressure. Deviations from these characteristics may occur and will be illustrated in the following.

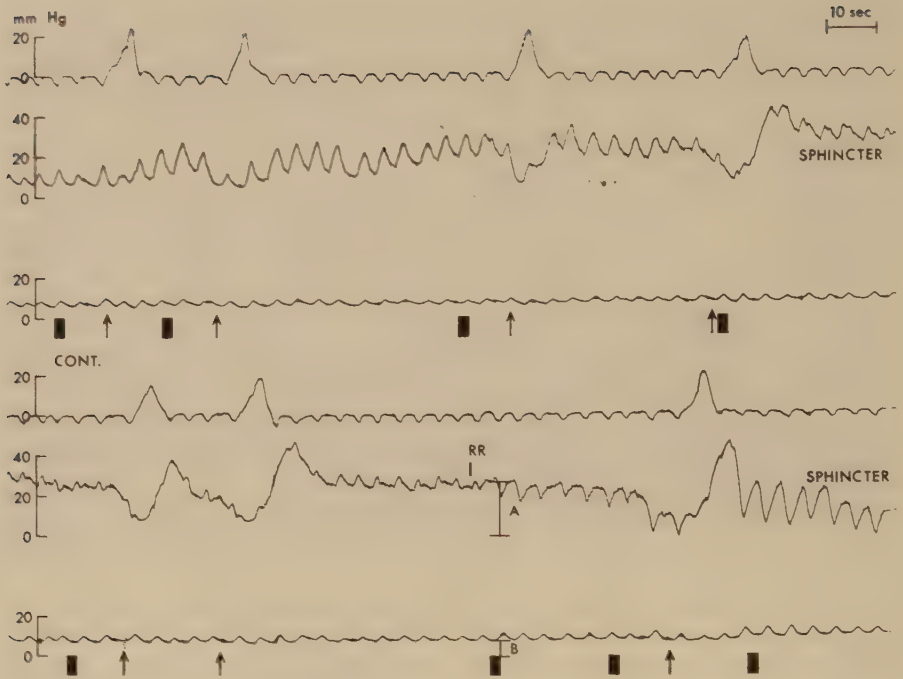


Fig. IV-7. Tracing made with intermittent withdrawal and swallowing on each level. In this as well as in the following figures each swallow is indicated by an arrow.

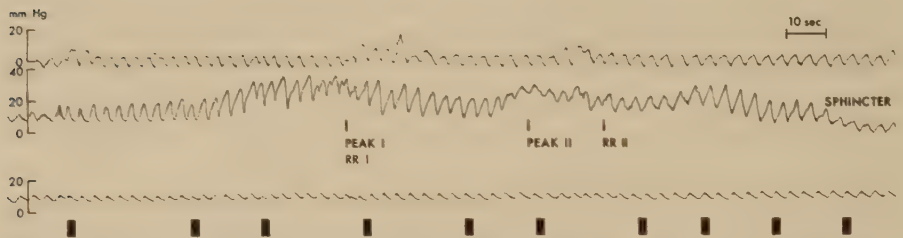


Fig. IV-8. Tracing that illustrates double peak of pressure and double respiratory reversal.

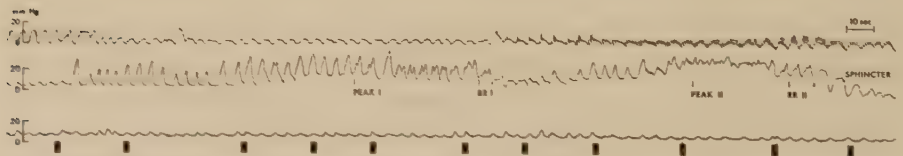


Fig. IV-9. Tracing that illustrates double peak of pressure and double respiratory reversal.

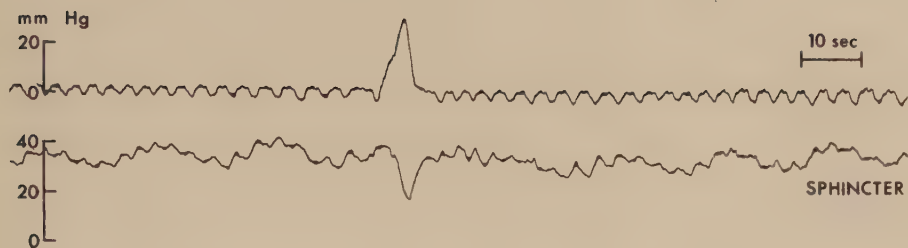


Fig. IV-10. Tracing that illustrates regular variations in sphincter pressure with a frequency of 3 to 4 per min.

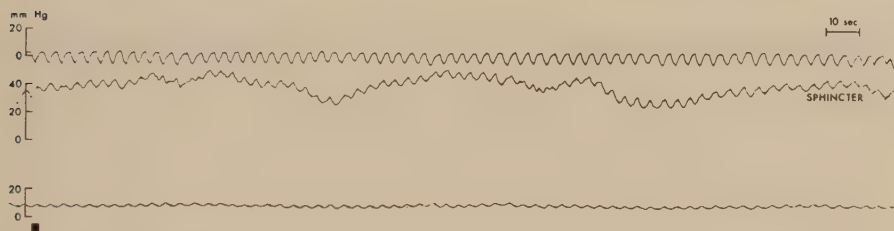


Fig. IV-11. Tracing that illustrates longer lasting variations in sphincter pressure.

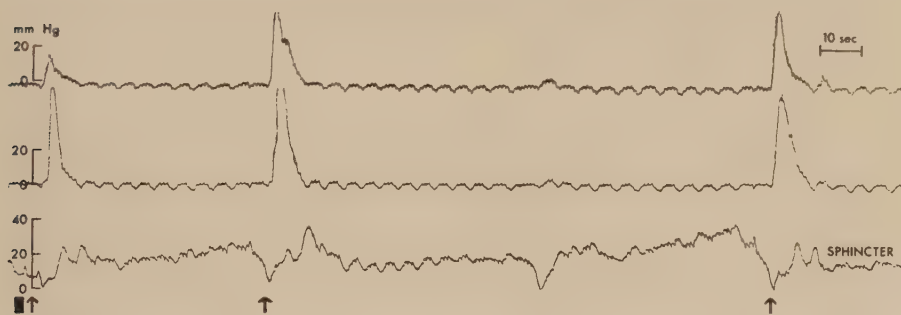


Fig. IV-12. Tracing that illustrates slowly increasing rise in sphincter pressure.

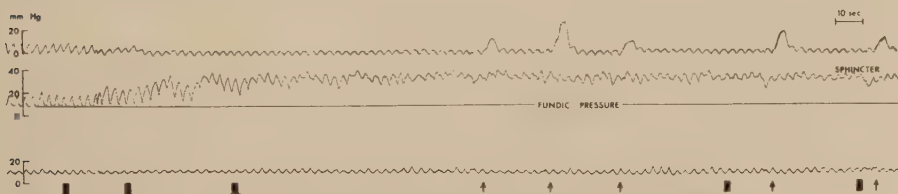


Fig. IV-13. Tracing that illustrates insufficient relaxation of the sphincter on swallowing.

Fig. 8 and fig. 9 show tracings in which the maximum pressure is not a plateau but appears as two separate maxima – double peak of pressure. In the same tracings the reversal from abdominal to thoracic respiratory de-

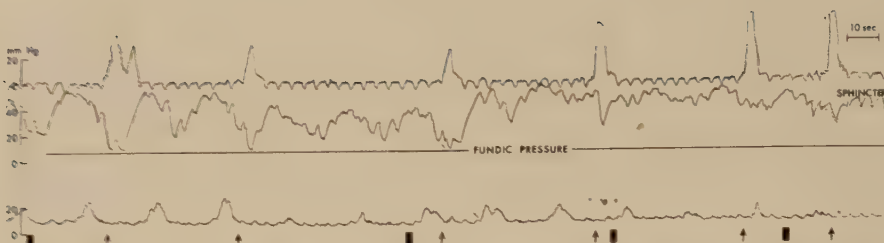


Fig. IV-14. Tracing that illustrates simultaneous and regular variations in intragastric and sphincter pressure.

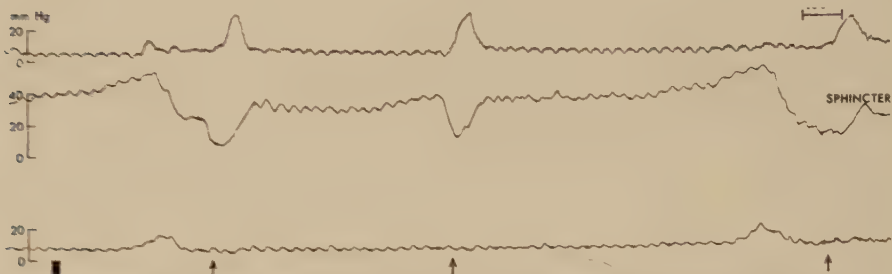


Fig. IV-15. Tracing that illustrates isolated and simultaneously occurring increases in intragastric and sphincter pressure.

flections occurs twice. This configuration is called double respiratory reversal.

In cases with regular variations in sphincter pressure the frequency is usually between 3 and 4 per min as shown in fig. 10. In fig. 11 the pressure variations are of longer duration and not as regular. The tracing in fig. 12 is characterized by a slowly increasing rise in pressure followed by swallowing, and then a repetition of the course. When reading tracings of this type the maximum end-expiratory pressure is also used.

On swallowing the normal sphincter relaxes to close to fundic pressure. Fig. 13 shows a case with insufficient relaxation.

Intragastric pressure is usually recorded as a constant pressure but occasionally simultaneous variations occur in intragastric and sphincter pressure. An example of regular pressure variations is shown in fig. 14. Fundic pressure is marked on the middle curve, and relaxation is seen to be insufficient in that segment of the sphincter in which pressure is maximum. Fig. 15 shows two isolated and simultaneous rises in intragastric and sphincter pressure.

With regard to abnormalities in the corpus of the esophagus on swallowing fig. 16 illustrates the type that is related to spastic esophagus and characterized by repetitive single contractions which may be simultaneous on different levels.

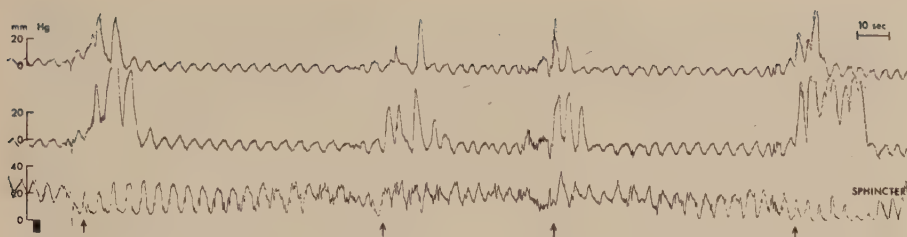


Fig. IV-16. Tracing that illustrates repetitive contractions of the corpus of the esophagus.

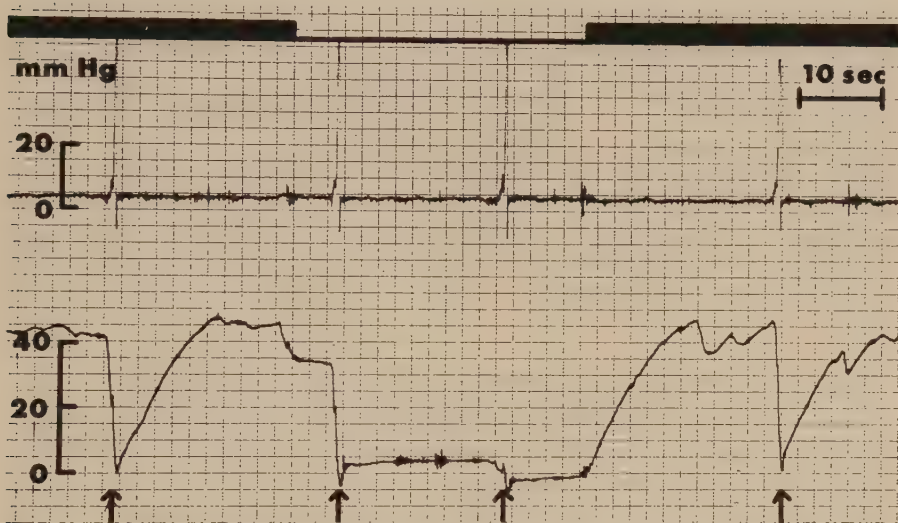


Fig. IV-17. An illustration of the importance of using flow by pressure recording. The upper curve is from the pharynx and the lower one from the pharyngoesophageal sphincter. In the interval between the two vertical bars the flow was discontinued. For further explanation see text.

As an appendix to this description of curves two tracings are shown which both illustrate the importance of the use of flow by pressure recordings. The problems are the same whether it be the question of recording from the upper or lower sphincter but, because of the more rapid pressure variations in the pharyngoesophageal sphincter it was chosen to use tracings from the latter as an example. To the left in fig. 17 is seen a normal relaxation on swallowing. After discontinuing the flow swallowing elicits a drop in pressure but the subsequent rise in pressure does not occur. The next swallowing does not elicit changes but after resuming the flow the pressure returns to its previous level, and swallowing now elicits the normal pattern. The importance of the flow rate by recording of rapid pressure variations is demonstrated

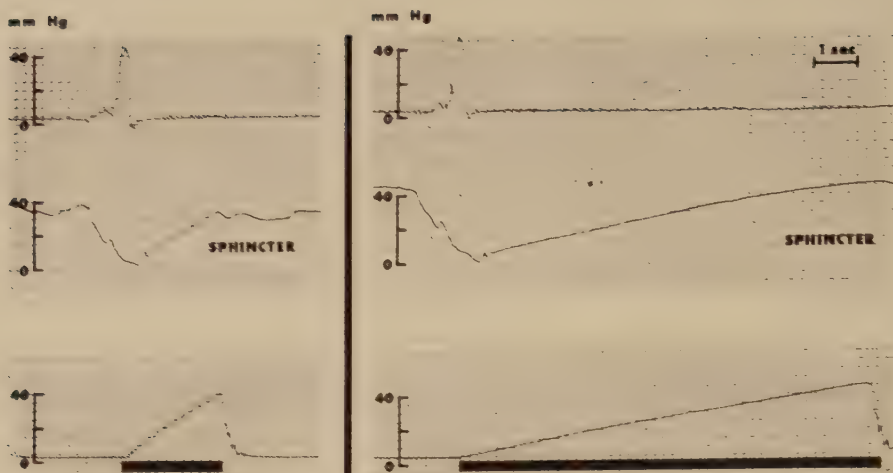


Fig. IV-18. An illustration of the importance of the flow rate by recording of rapid variations in pressure. The two curves at the top are from the pharynx and the pharyngoesophageal sphincter, respectively. The bottom curves are artificial, showing the increase in pressure per time unit on blocking the opening of the catheter. By the two recordings to the left the flow rate was 0.4 ml per min, whilst by those to the right it was 0.1 ml per min.

in fig. 18. On blocking the opening of the catheter an increase in the flow rate cause a major pressure increase per time unit, and this is also demonstrated in relation to closure of the sphincter following relaxation. Since the segments of the curves are parallel to the corresponding artificial curves, duration of relaxation is recorded as being shorter at a higher flow rate.

A pressure recording system can be described mathematically by a second order differential equation, and the complete system is characterized by two variables, — the degree of damping, and — the undamped natural frequency (Hansen, 1949). To estimate these characteristics the response of the present system to sudden changes in pressure was determined. On the basis of several measurements it was found that the degree of damping (α) was 2.8 ± 0.11 (mean $\pm$ SD) and the undamped natural frequency 0.377 Hz. Additionally, it was found that the mean ds/dt for an increase in pressure from zero to 50 mm Hg was 6.7 mm Hg per sec. This means that the present system is heavily damped and that only pressure signals with a low frequency can be transmitted with correct amplitude and phase.

Statistical methods

If the size and composition of the materials permitted it, the statistical analyses were initiated by a comparison between the present and the normal

distribution. This test was performed as described by Hald (1952) (p. 742) and, in cases in which the p-value was higher than 0.025 it was accepted that the distribution might be normal. Therefore, in the following calculations, parametric as well as non-parametric statistics were used. For materials not fulfilling the condition of making this analysis, non-parametric statistics were used. Conventional methods within parametric and non-parametric statistics have been used, and a p-value less than 0.05 has been accepted as significant. When using parametric statistics in analysis of the difference between means, where the analysis of the variance ratio rejects that the variances are the same, the modification of the t-test that was described by Hald (1952) (p. 402) was used. The corresponding p-value is stated as p_{atu} .

Statistical symbols

n:	number of cases
s^2 :	variance
SD:	standard deviation
SE:	standard error of the mean
CV:	coefficient of variation
r:	coefficient of correlation
r_s :	Spearman's coefficient of correlation
p_{tu} :	p-value for the unpaired t-test
p_{atu} :	p-value for the approximated unpaired t-test
p_{MW} :	p-value for the unpaired rank sum test (Mann-Whitney)
p_w :	p-value for the paired rank sum test (Wilcoxon)
$p\chi^2$:	p-value for the chi-square test

Patient material

The material comprises ambulatory patients and patients admitted to Odense University Hospital. By far the majority were from the Department of Gastrointestinal Surgery K, the Department of Medical Gastroenterology S and the Department of Thoracic and Cardiovascular Surgery T. The rest were from the Departments of Medicine B, C and M.

The separate groups of the total material consists of patients suffering from commonly occurring diseases of the upper abdomen. It became obvious already at the start of the study that it would be impossible to make a manometric study of all patients. Thus there has been a selection due to the capacity of investigation but, this does not imply a deliberate selection of certain subgroups with the materials. The practice was that in periods with many patients fulfilling the criteria for acceptance in one of the groups, the

choice fell primarily on those belonging to groups which were supposed to be most poorly represented in the finished work.

Beyond an undesigned selection brought about because of the limited investigation capacity, there has also been a deliberate selection based on three criteria. Of these I laid down two, whilst the third was decided by factors that could not be controlled. The three criteria were the following:

1. Patients of advanced age or with poor cerebral function were excluded. This criterion was chosen because the method of investigation called for close cooperation between patient and investigator but, as the work was getting on and my experience grew it was not used as often as in the start.

2. Patients in poor general condition, or with severe complicating disorders were excluded from the study. The same applied to patients under treatment with drugs known or supposed to influence sphincter pressure.

3. As the method of investigation became known and the results reported, my colleagues from other departments chose their own indication for the manometric investigation. The result was that the Department of Thoracic and Cardiovascular Surgery T received many requests to examine patients by the manometric method, particularly in the last year of the study. All requests were complied with, and the great majority of the patients fulfilled the criteria for acceptance in one of the groups of the material. There is, however, a theoretical possibility that other doctors' indications may have biased the representation of certain subgroups within the separate materials.

To ensure the greatest possible diagnostic certainty rather rigoristic criteria were laid down for division of the material into subgroups. In operated patients the surgical diagnosis was decisive irrespective of the results of the radiological examinations and endoscopies. As for the non-operated patients there was a few instances with a discrepancy between the radiological and the endoscopic findings; provided that the entire gastric mucosa had been examined by gastroscopy the results of this examination was decisive for the diagnosis.

The manometric studies were made with the patients fasting. Most of the studies were made before noon with the patient having fasted from the preceding day. When the studies were made in the afternoon, the patients had been fasting for at least five hours. All patients were free from pain when studied. In the group of patients who were studied both before and after operation the time of observation after operation varied. This was due to the fact that processing of the results from the groups, for which follow-up studies had been planned already from the start, gave rise to follow-up studies of other groups. It also contributed to the variation in time of observation that at the termination of the project an attempt was made to reexamine those patients who had defected from the first postoperative follow-up examination.

	n	Mean	Range	s ²	pχ ²
Sphincter pressure (mm Hg)	41	15	9–23	13.8	0.30)p>0.20
Sphincter length (cm)	41	2.9	1.5–4.5	0.45	0.80)p>0.70
Age (years)	41	30	20–65	–	0.01)p>0.001
Weight (% of normals)	41	÷ 4	÷ 26–+ 36	154.6	0.50)p>0.40

Table IV–I. The various characteristics of the normal material.

As regards the symptoms heartburn and dysphagia, they are defined as follows. Heartburn – a burning sensation behind the sternum which is accentuated in the lying position and on stooping. Dysphagia – a sensation of the food stopping up behind the lower part of the sternum.

From December, 1970, to October, 1973, a total of 1061 manometric studies were made of 784 patients and normal subjects. All studies were made by the author. The materials which are presented in the following chapters have been selected from the total material, and the criteria for selection are stated in each chapter.

Normal material

In the period from December, 1970 to March, 1973, manometric studies were made of 42 subjects, who had been accepted as normal. The 29 were healthy individuals and the remaining 13 were admitted with minor surgical diseases without relation to the esophagus or the remaining part of the gastrointestinal tract. In one case the recording was technically unsatisfactory, and the processed material thus comprises 41 subjects, of whom 29 were women and 12 men.

The characteristics of this material appear from table I. Pressures between 8 and 22 mm Hg (mean $\pm$ 2 SD) were accepted as normal. A pressure of more than 22 mm Hg was accepted as hypertensive. It was investigated whether there might be a relationship of sphincter pressure to sphincter length, but this could not be demonstrated. Moreover, a regression analysis

Test no.	Sphincter Pressure (mm Hg)		Difference
	Catheter I	Catheter II	
1	15	14	1
2	14	17	3
3	14	15	1
4	19	18	1
5	18	15	3
6	20	19	1
7	15	18	3
8	18	20	2
9	18	20	2
10	18	17	1
11	21	21	0
12	21	19	2
Mean	18	18	
SD	2.5	2.2	
CV	0.14	0.12	

Table IV-II. Characteristics of sphincter pressures from 12 studies of the same individual. Catheter I and II had side-holes at the same level.

was made of the relationship of sphincter pressure to sex, age and weight compared to the normal weight. The regression coefficient are not significant.

Reproducibility

The problems with regard to reproduction and the importance of the location of the side-holes were subjected by 12 studies of the same individual. The studies were made by means of a pressure probe consisting of three catheters, of which two had the side-holes placed on the same level but with an angle of 160 to 180 degrees between the side-holes. The studies were carried out on different days and over a period of two months.

The characteristics of sphincter pressures in this study are stated in Table II.

Discussion

On the evidence of the findings in the model studies mentioned in chapter II two conclusions may be drawn: First, – a reliable recording requires a constant flow through the catheters; second, – the flow rate is of no consequence at slow variations in pressure but of great importance at rapid variations (Pope, 1967; Winans and Harris, 1967; Rinaldo and Levey, 1968; Pope, 1970; Dodds *et al.* 1972a; Waldeck *et al.* 1973). This means that the flow rate used in the present study allows recording of fundic pressure, resting sphincter pressure, fall in sphincter pressure on relaxation and resting pressure in the corpus of the esophagus whilst, on the other hand, it does not allow recording of rapid variations in pressure and therefore is unsuitable for the evaluation of the duration of sphincter relaxation and the amplitude of the peristaltic contractions in the corpus of the esophagus.

As regards the technique of investigation there are three possibilities to choose from: First, – intermittent withdrawal without swallowing, the so-called “pull-through” technique; second, – intermittent withdrawal with swallowing at each level; third, – continuous withdrawal without swallowing. At the start of the study it was intended to employ the two first mentioned techniques in all patients but, as the work was getting on it became clear that this was not neither possible nor desirable. The “pull-through” technique is based on 10 to 15 sec recording at each half cm, meaning that such a study will take about 2 min. Young and well-cooperating patients may be able to avoid swallowing for a period of this length but it is not possible to employ this technique on a larger patient material. Moreover, the initial studies revealed that the “pull-through” technique was insufficient. Maximum sphincter pressure is not always a constant plateau but may display more or less regular variations, and therefore a recording of 10 to 15 sec duration at each level is not enough.

The third technique – continuous withdrawal – was used by Rinaldo and Levey (1968), Kaye and Showalter (1971), Winans (1972a) and Waldeck *et al.* (1973). This technique requires a considerable greater flow rate, and the procedure differs in several respects from that described above. The study is made with the patient holding his breath in the expiratory state, and the withdrawal is continuous and more rapid. Rinaldo and Levey (1968) used both this and the “pull-through” technique in ten patients. They found that the mean pressure obtained by continuous withdrawal was midway between the end-expiratory and end-inspiratory pressure by the “pull-through” technique. However, the results showed an appreciable dispersion, the reason of which is supposed to be that the patients stopped breathing at various stages in the respiratory cycle. In this context it should be emphasized that spontaneous variations in sphincter pressure are not recorded by this method.

Intermittent withdrawal with swallowing at each level was chosen as the routine method for the greater part of the present material. In accordance with the above argumentation this method has the principal advantage that it may be applied on a varied patient material, and that it records the spontaneous variations in sphincter pressure.

In the published normal materials there are considerable mutual differences in mean sphincter pressure and in standard error of the mean. These differences are evident from table III listing the most important characteristics of the largest normal materials. There are at least three reasons for these differences. The first is the size and composition of the materials, the second is the procedure used for reading the curves and the third is the differences in the construction of the pressure probe.

Most materials are small and not published as normal materials but form the basis of technological and pharmacological investigations. In most cases the information on the criteria for acceptance in the normal material is incomplete but, it is obvious that most often they include both subjects without any symptoms at all and patients. It is a common demand that the patients must not have symptoms referable to the esophagus but with our present knowledge of the regulation of sphincter pressure the demands should be more rigorous.

With regard to the reading of the curves many materials are without indication of the practice that has been followed. As will be seen from the illustrations in this chapter, the maximum sphincter pressure is not always a constant plateau but may display more or less regular variations. In consequence, the height of the pressure will be dependent on where the reading is made. As mentioned before, I have chosen the segment where the pressure is highest regardless of the form of the curve. Likewise it is of importance that different levels are used in relation to the respiratory deflections. A group of American investigators have chosen to define sphincter pressure as the mean between end-expiratory and end-inspiratory sphincter pressure less the mean pressure in the stomach (Pope, 1967; Castell and Harris, 1970; Cohen and Harris, 1971; Cohen and Lipshutz, 1971a; Dennish and Castell, 1972; Nebel and Castell, 1972a; Roling, Farrell, and Castell, 1972). This will usually result in recording of higher values than when reading at end-expiration and, as the rise in pressure on inspiration must be regarded as a rapid change in pressure, it will also mean that the resting sphincter pressure will depend on the flow rate.

The major cause of the divergencies between the various normal materials will no doubt be differences in the construction of the probes. The gastroesophageal sphincter defines a closed compartment, and every recording involves a dilatation and with it a stretch of the muscles. As demonstrated by Lipshutz and Cohen (1971) muscle from the sphincter area has

Authors	No. of cases	Mean	SE
Butterfield, Struthers, and Showalter (1972) ..	14	10.5	3.1
Castell and Harris (1970)	18	15.0	1.7
Cohen and Harris (1971)	25	20.4	1.1
Cohen and Lipshutz (1971a)	20	19.4	1.3
Csendes and Larrain (1972)	30	11.0	0.7
Dennish and Castell (1972)	7	18.0	2.8
Dilawari, Blendis, and Edwards (1973)	17	17.2	1.5
Fox, Vidins, and Beck (1970)	10	16.1	—
	10	11.4	—
Heitmann and Möller (1970).....	48	10.5	0.5
Nebel and Castell (1972a)	10	15.9	1.9
	10	16.9	2.3
	10	22.0	2.1
Pope (1967)	15	24.8	2.5
Reid, Hogan, Dodds, Soergel, and Arndorfer (1972)	23	15	1.5
Resin, Stern, Sturdevant, and Isenberg (1972)..	7	14.9	0.7
Rinaldo and Levey (1968)	10	10.9	2.5
	10	12.4	1.9
Roling, Farrell, and Castell (1972)	11	14.6	1.3
Present material	41	15	0.6

Table IV-III. A survey of the most important characteristics from previously reported normal materials.

special length tension characteristics. As compared with muscle from the antrum and the corpus of the esophagus it develops a greater peak active tension, and requires less stretch to reach its optimal length. Therefore it is to be expected that the diameter of the probe is of greatest importance to the height of the pressure that is recorded. That this is really so has been demonstrated by Biancani *et al.* (1973), who state that the relationship of muscle wall tension T to intraluminal pressure P follows Laplace's law: $P = Tt/R$, according to which t indicates the thickness of the circular layer of muscle and R the radius. As compared with the basal condition the presence of a pressure probe will cause changes in primarily T and R , and P will be dependent of the changes in the mutual relation between these two factors. These theoretical considerations have been applied by the recording of pressure in humans with a competent sphincter. The recordings were made by means of four different probes, the diameter of which was 2.5, 5.0, 7.5 and 10 mm, respectively. With the smallest diameter the mean pressure was 23 mm Hg, with the intermediate diameter it decreased to 17 mm Hg whilst a further increase in diameter to 10 mm was followed by an increase in mean pressure to 33 mm Hg. It was concluded that with a gradual increase of the

diameter of the probe the effect of R will initially be greater than that of T but later the opposite will be the case.

All these factors considered, the present material may best be compared with those reported by Heitmann and Möller (1970) and Csendes and Larrain (1972). The materials are of fairly the same size, there are but minor differences in the technical apparatus and the way in which the studies are carried out, and reading of the curves has been made on the same guidelines. A common feature of the material reported by Heitmann and Möller (1970) and the present one is that it has not been possible to demonstrate any relationship of pressure to sex and age, respectively.

With the procedure followed in the present work sphincter pressure can be reproduced with a coefficient of variation of 0.12 to 0.14. Beck, Fox, and Vidins (1971) also investigated the reproducibility of sphincter pressure and found a coefficient of variation of 0.30. However, the results of the two studies are not directly comparable. Beck *et al.* (1971) do not mention what procedure they followed by recording of the curves, neither does it appear whether by reading of the curves they made allowance for the previously mentioned spontaneous variations in pressure. It is an absolute condition of an optimal reproduction that the pressure recordings from each segment of the sphincter are of a sufficiently long duration to also register possible spontaneous variations in pressure. Because of these variations it is also necessary to define precisely the guideline followed by reading of the curve.

The importance of the location of the side-holes for the pressure recording has also been investigated previously. Kaye and Showalter (1971) used a probe consisting of a pH electrode and three catheters with side-holes on the same level but with different radial orientation. Winans (1972) used a probe consisting of eight catheters, the side-holes of which were spaced at intervals of 45 degrees about the circumference of the probe. Both investigations showed differences in the pressure recorded with the single catheters. Winans (1972) found that the pressure recorded from holes directed to the patient's left and left posterior were significantly greater than those directed to the other six directions. He concluded that the predominance of pressures recorded from the left posterolateral direction suggests that in normals an extrinsic force from this direction – possibly the lateral margin of the diaphragmatic hiatus – augments the pressure resulting from the sphincter. The results of the present study confirm that the pressures recorded with two side-holes on the same level are different, although the difference is small and not systematic; it is not the same side-hole that constantly gives an either lower or higher value than that recorded with the other side-hole. The difference between the results of the above mentioned studies and the present one may be ascribed to differences in the construction of the pressure probe. Both Kaye and Showalter (1971) and Winans (1972) used a probe

with greater diameter and considerably greater weight. Due to the anatomical structure of the gastroesophageal region particularly the weight of the pressure probe will be of importance. The catheter whose side-hole is directed posteriorly will in certain situations record not only the sphincter pressure but also the weight of the probe. This is most likely to explain why Winans (1972) could demonstrate a significantly higher pressure with the catheter whose side-hole was directed posteriorly. It is a fact, however, that irrespective of the diameter of the probe there are differences in the pressures recorded with the different catheters, and it is possible that a better reproducibility may be obtained by using a single catheter with more side-holes on the same level.

Certain deviations from the common curve pattern, as for example double peak of pressure and double respiratory reversal, have been used by several authors as being diagnostic for the presence of a hiatus hernia of the sliding type (Code, Kelley, Schlegel, and Olsen, 1962; Schmidt, Jones, Hunt, Code, Anderson, and Andersen, 1962; Sandmark, 1963; Wankling, Warrian, and Lind, 1965; Crispin, McIver, and Lind, 1967; Garrett and Godwin, 1969; Lockwood and Borgeskov, 1969; Haddad, 1970; Skinner and Booth, 1970; Butterfield, Struthers, and Showalter, 1972; Habibulla, 1972). In cases with double peak of pressure the lower peak is supposed to be caused by compression of the diaphragm, and the upper one by the gastroesophageal sphincter. As regards double respiratory reversal the arguments are the same. The transition from abdomen to thorax is held responsible for the lower and the sphincter for the upper reversal.

Animal and human experiments of recent years have demonstrated, however, that these theories are correct only in part. Mann, Ellis, Schlegel, and Code (1964) studied the effect of abdominal displacement of the canine gastroesophageal sphincter on sphincter profile. The operation involved transection of the phrenicoesophageal ligament and reattachment of the esophagus to the diaphragm six centimeters above the gastroesophageal junction. The profile was clearly changed postoperatively, and in all cases there were two peaks of pressure, of which the lower pertained to the sphincter and the upper to the attachment of the esophagus to the diaphragm. Greenwood, Schlegel, Helm, and Code (1965) studied the effect of an operatively constructed hiatus hernia on sphincter profile in dogs. The pressure was recorded using balloon technique and non-perfused catheters. All recordings from the intact dogs showed only one respiratory reversal and one peak of pressure. In the cases with hiatus hernia there was more than one respiratory reversal in about a third of the recordings. Two peaks of pressure were seen in about 25 per cent of the recordings. Lind, Cotton, Blanchard, Crispin, and Dimopolos (1969) studied the effect of displacement of the sphincter into the thorax of dogs. The pressure profile was clearly changed post-

operatively. Usually there were two zones of elevated pressure, the lower one on the level of the diaphragmatic hiatus, and the upper one on the level of the gastroesophageal junction. In the recordings that did not demonstrate a zone of increased pressure at the diaphragm, a double respiratory reversal was often demonstrated. These deviations were not present in the preoperative recordings. Garrett, Godwin, Falkenberry, and Shoemaker (1970) studied the sphincter profile in seven normal opossum. In all cases there was a double peak of pressure, and in five cases also double respiratory reversal. The anatomical localization of the peaks was determined by palpation on open abdomen, and the lower peak corresponded to the gastroesophageal junction and the upper one to the diaphragm.

Summing up, the results of these investigations demonstrate that double respiratory reversal and double peak of pressure may, in some cases, be ascribed to anatomical changes by the way of proximal discolation of the gastroesophageal region, whilst in others one has to accept that these variations occur in connection with normal anatomical conditions.

The same conclusion may be drawn from human studies. In this context it is of interest that Harris and Pope (1966) demonstrated that occasionally respiratory reversal may be associated with the sphincter instead of with the diaphragm. Their studies were carried out in a model of the esophagus and in normals and patients with hiatus hernia. In addition they found that the reversal was not a fixed point but could be located at a variable point along the length of the sphincter. These studies lend support to the theory that a dislocated sphincter may be responsible for the upper respiratory reversal. Kaye and Showalter (1971) investigated the sphincter profile of 15 normal human subjects. In eight they found a double respiratory reversal, and in all but one the double reversal appeared in only one of the three leads. Double peak of pressure was also common. Fox, Vidins, and Beck (1970) reported similar results from a study of ten normal subjects. They found a double peak in one lead in five subjects. Even though these normal materials were not examined radiologically it must be regarded as unlikely that hiatus hernia should occur with such a high frequency, and one has therefore to accept that deviations from the normal curve pattern may have a non-organic cause.

The term "double peak of pressure" implies that the sphincter has a stationary pressure profile, meaning that in a certain segment the pressure must be constant within a reasonable time interval. However, the present and several previously reported materials demonstrate that this condition is not fulfilled. Carlson, Boyd, and Percy (1922) described regular variations in the sphincter pressure in dogs. Lind, Duthie, Schlegel, and Code (1961) studied pressures in the sphincter and fundus of dogs. The recordings from the fundus showed well-marked phasic changes of pressure, and similar and

simultaneous changes were seen in the recordings from the sphincter. The regular pressure variations were particularly clear in the lower part of the sphincter and less frequent and not so marked in the upper part. Bloom, Stekelman, Varadee, Carvajal, and Davidson (1971) studied sphincter pressure in 27 normal human subjects and recorded pressures over a longer space of time. They used perfused catheters, and the pressure probe was placed in such a way that one side-hole was stationary in a certain segment of the sphincter. In some cases a protracted decline in pressure was reversed by swallowing, mechanical stimulation or perfusion of the gastric fundus. In others a transient rapid drop resembling a typical response to swallowing, but not preceded by peristalsis was seen. These characteristics also occur in the present material but the more or less regular variations in pressure were by far more frequent. It was also a common feature that pressure variations were most pronounced in the lower part of the sphincter.

These spontaneous variations within a smaller segment of the sphincter is also a major cause of the confusion in the literature with regard to profile abnormalities. A "pull-through" investigation as it is usually carried out will not give a reliable impression of these variations, and the sphincter pressure will depend on the phase in which the investigation is made. By slow, intermittent withdrawal, or by recording with the probe in a stationary position, it will be possible in certain cases to record as many peaks as desired. It is also owing to these variations in pressure that by repeated "pull-through" studies it will be possible to record different profiles and with them different sphincter pressures.

CHAPTER V

Gastroesophageal sphincter pressure in patients with dyspepsia without organic cause

Introduction

Despite the technological advances of late years and the ensuing refinement of the diagnostic aids, patients suffering from dyspepsia without any demonstrable cause still constitute an appreciable proportion of the gastroenterological clientele. At the present stage of our knowledge of the pathophysiological conditions, both the medical and the surgical treatment rest on inadequate foundations, and the results have not been impressive either. This group of patients is supposed to be heterogenous and to comprise diseases of different etiology and pathogenesis, and I have therefore taken an interest in investigating whether manometric studies might contribute to a classification into smaller and more well-defined disease entities.

Material

The criteria for acceptance were based on the clinical picture and the results of the diagnostic examinations. All patients admitted to the study fulfilled the following conditions:

1. Periodic attacks of upper abdominal pain
2. No previous upper abdominal operations
3. Radiological examination of the esophagus, stomach, and duodenum undertaken
4. No demonstrable organic cause of the dyspepsia

In the period from December, 1970, to March, 1973, manometric studies were made of 100 patients. The recordings proved technically unsatisfactory in two cases, and the processed material thus comprise 98 cases – 56 women and 42 men. Ages varied from 17 to 83 years, mean age 48 years.

The distribution of symptoms is shown in table I, and table II lists the diagnostic programme.

After the manometric study five patients underwent exploratory laparotomy or abdominal surgery. There were no demonstrable organic changes.

Method

The *manometric studies* were carried out as described in chapter IV.

Results

Fig. 1 lists the sphincter pressures of the total material, in patients with heartburn (group A), and in patients with dysphagia (group B). The two patients with heartburn and dysphagia have not been included in any of the two subgroups. Table III shows the characteristics of sphincter pressure in the corresponding groups. In the total material there were 54 with a pressure within the normal area, 17 had a pressure below the lower limit of normal, whilst 27 had a pressure that is higher than the upper limit of normal. In group A mean pressure is lower than in the normal material ($0.01 > P_{MW}$), and in group B it is higher than in the normal material ($0.01 > P_{MW}$). Eleven of the 18 patients with heartburn (group A) had a pressure within the normal area. In patients without heartburn nine had a pressure that is below the lower limit of normal.

There were 25 cases of periodic dysphagia, and the occurrence of abnormalities in relation to swallowing in this group is shown in table IV. The corresponding figures in the group of patients without dysphagia is shown in table V. The frequency of abnormalities is significantly higher in the dysphagia group ($0.001 > p_{\chi^2}$).

Out of 27 patients with a pressure above the upper limit of normal, 14 had dysphagia. The occurrence of abnormalities in relation to swallowing among these 14 patients is shown in table VI. The corresponding figures in

Symptoms	No. of patients
Pain	55
Pain and heartburn	18
Pain, heartburn, and dysphagia	2
Pain and dysphagia	23
Total	98

Table V-I. The distribution of the various symptoms in the total material.

Diagnostic examinations	No. of patients
X-ray, – esophagus, stomach, and duodenum	98
X-ray, – biliary tract	62
X-ray, – colon	35
Esophagoscopy	31
Gastroscopy	64

Table V-II. The diagnostic programme in the total material.

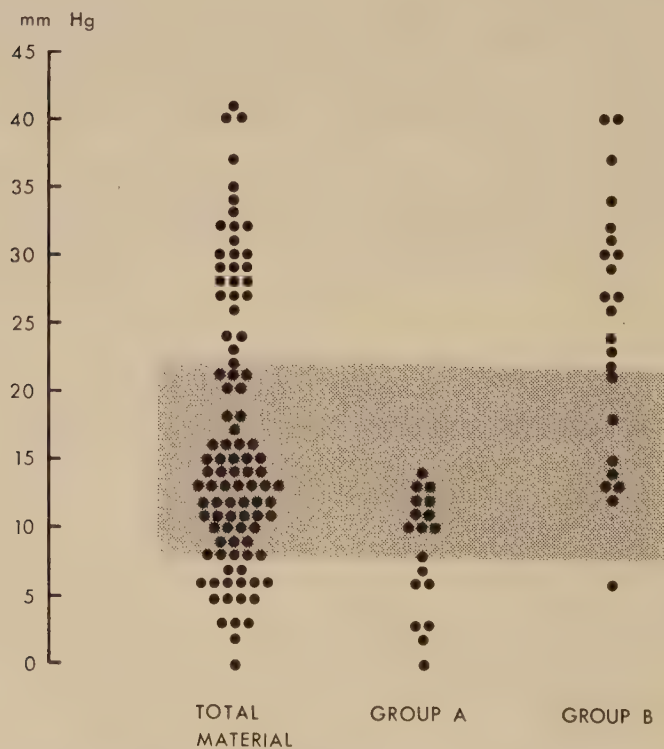


Fig. V-1. Each sphincter pressure of the total material, in patients with heartburn (group A), and in patients with dysphagia (group B).

	n	Mean	Range	$p\chi^2$
Total material	98	17	0-41	0.005)p>0.001
Group A	18	8	0-14	—
Group B	23	25	6-40	—

Table V-III. Characteristics of sphincter pressure (mm Hg) of the total material, in patients with heartburn (group A), and in patients with dysphagia (group B).

Abnormalities	No. of patients
Insufficient sphincter-relaxation	6
Spastic esophagus	9
Insufficient sphincter-relaxation and spastic esophagus	5
Total	20

Table V-IV. The occurrence of abnormalities in relation to swallowing in 25 patients with dysphagia.

Abnormalities	No. of patients
Insufficient sphincter-relaxation	4
Spastic esophagus	3
Insufficient sphincter-relaxation and spastic esophagus	0
Total	7

Table V-V. The occurrence of abnormalities in relation to swallowing in 73 patients without dysphagia.

the group of patients with hypertensive sphincter and no dysphagia is shown in table VII. The frequency of abnormalities is significantly higher in the dysphagia group ($0.05 > p_{\chi^2}$).

Discussion

In the present material of patients with dyspepsia without any demonstrable organic cause, sphincter pressures are spread both inside and outside the limits of normal. In 54 out of 98 patients the pressure was of the same magnitude as in normal subjects, whilst in 17 it was below the lower limit, and in 27 over the upper limit of normal. This means that in about half the patients the pathophysiological conditions did not involve changes in resting gastroesophageal sphincter pressure.

However, it is reasonable to assume that the material comprises diseases of different pathophysiology. The diagnostic programme does not allow further differentiation and one has to accept that the material is inapplicable for calculations as a whole.

From the total material it is possible to separate two disease entities, the pathophysiology and clinic of which it has previously been attempted to correlate to the results of the manometric studies. One is low pressure and heartburn, the other high pressure and periodic pain.

It is generally agreed that by far the most frequent cause of spontaneous heartburn is the contact between acid and the esophageal mucosa. In patients with heartburn the symptoms can be reproduced by perfusion of the lower part of the esophagus with acid (Bernstein and Baker, 1958; Tuttle, Bettarello, and Grossman, 1960; Tuttle, Rufin, and Bettarello, 1961; Siegel and Hendrix, 1963; Atkinson and Bennet, 1968), and many authors have demonstrated that these patients have – intermittently or permanently – a low pH in the lower part of the esophagus (Tuttle and Grossman, 1958; Tuttle *et al.* 1960; Tuttle *et al.* 1961; Besancon, Baujat, and Debray, 1962; Van Derstappen and Texter, 1964; Piccone, Gutelius, and McCorriston, 1965; Borgeskov, Lockwood, Bertelsen, and Hasner, 1966; Skinner and Camp, 1968; Kantrowitz, Corson, Fleischli, and Skinner, 1969; Lockwood and Borgeskov, 1969; Aune and Norman, 1970; Haddad, 1970; Ismail-Beigi, Horton, and Pope, 1970; Skinner and Booth, 1970; Rudolph, Herrera, Stein, and Roth, 1971; Benz, Hootkin, Margulies, Donner, Cauthorne, and Hendrix, 1972; Butterfield *et al.* 1972). Two different methods of investigation were used, and both were initiated either by installation of hydrochloric acid into the stomach, or stimulation with histamine of the gastric acid secretion. One method is a withdrawal procedure by which an assembly consisting of a pH electrode and a catheter with an opening at the level of the electrode is withdrawn from the stomach through the sphincter and into the corpus of the

Abnormalities	No. of patients
Insufficient sphincter-relaxation	4
Spastic esophagus	3
Insufficient sphincter-relaxation and spastic esophagus	3
Total	10

Table V-VI. The occurrence of abnormalities in relation to swallowing in 14 patients with hypertensive sphincter and dysphagia.

Abnormalities	No. of patients
Insufficient sphincter-relaxation	3
Spastic esophagus	0
Insufficient sphincter-relaxation and spastic esophagus	0
Total	3

Table V-VII. The occurrence of abnormalities in relation to swallowing in 13 patients with hypertensive sphincter and no dysphagia.

esophagus. By this method changes in pH are recorded in relation to the distance from the respiratory reversal. The other method is a recording of the pH proximally to the sphincter area both at rest and in relation to a series of provocative manoeuvres to induce reflux. The results demonstrated that reflux may occur both in normal subjects and in patients with heartburn but that it is considerable more frequent in the patient group. A few of the mentioned authors used perfused catheters, and the outcome of their studies will later be dealt with in more details. It should be emphasized, however, that in the light of our present knowledge a modification of this method would be chosen. Sphincter pressure is controlled by the acidity of the gastric contents, and an artificial increase in acidity by installation of hydrochloric acid will reduce the pressure. This was first demonstrated by Castell and Harris (1970) who investigated the effect of installation of 0.1 n hydrochloric acid into the sto-

mach on sphincter pressure. When the gastric hydrogen ion concentration was raised to approximately 100 m-equiv per l, pressure decreased by a mean of 12.8 mm Hg. These results have been reproduced by Cohen *et al.* (1971) and Cohen and Lipshutz (1971), and it means that by using this procedure one reduces the strength of the factor, the effectivity of which one wishes to evaluate.

Contact between the gastric secretion and the esophageal mucosa implies that the barrier between the two organs is incompetent. Cohen and Harris (1970) demonstrated that the resistance against reflux from the stomach through the sphincter and into the corpus of the esophagus is directly correlated to sphincter pressure, recorded by perfused catheters. In cases with heartburn, sphincter pressure could therefore be expected to be low. On the evidence of the present and previous reports this is correct only in part. Pope (1967) compared sphincter pressures in 15 normal subjects with those in a group of ten patients with heartburn. In the normal group mean pressure was 24.8 mm Hg as compared to 11.6 mm Hg in the heartburn group. Although these values differ significantly there was a fair amount of overlapping between the individual values. Winans and Harris (1967) investigated 14 normal volunteers and seven patients with "grossly incompetent sphincter as indicated by free gastroesophageal reflux of barium". None of these patients had demonstrable hiatus hernia. They found a clear separation between sphincter pressure in these two groups. The mean resting pressure was significantly higher in the normal subjects, and there was no overlapping between the two groups. Haddad (1970) made a simultaneous study of sphincter pressure and intraesophageal pH measurements in ten controls and 58 patients. The studies were made after installation of 300 ml of 0.1 n hydrochloric acid into the stomach, and the patients were grouped according to the results of the pH measurements. Mean pressure in the control group was 13.2 mm Hg, and reflux was not demonstrated in any of these subjects. Patients with reflux on strain had a mean pressure of 6.9 mm Hg, and the group with free reflux had a mean pressure of 3.4 mm Hg. The abnormal groups had mean pressures that were significantly lower than in the control group, and patients with the most marked degree of reflux had the lowest sphincter pressures. Ismail-Beigi *et al.* (1970) used the same procedure in a study of 21 healthy subjects and 43 patients with heartburn. In the group of normal subjects the mean pressure was 25 mm Hg, and none of them demonstrated reflux. Thirty-three of the patients with heartburn demonstrated reflux with the pH test, and they had a mean pressure of 11 mm Hg. The remaining ten patients with heartburn had a negative pH test, and a mean pressure of 15 mm Hg. Although the mean pressures were different there was a great overlapping between the individual values in normale and patients with heartburn. Skinner and Booth (1970) performed manometry followed by

installation of acid into the stomach, and a pH reflux test. There was no significant difference in mean pressures between the groups of patients with or without "symptoms of gastroesophageal reflux". Forty patients with a negative pH reflux test had a mean pressure of 7.3 mm Hg, whilst the mean pressure in a group of thirty patients with a positive test was 3.7 mm Hg. These values are significantly different, but there was a considerable overlapping between the individual values in the two groups. Cohen and Harris (1971) investigated the resting sphincter pressure in 38 patients without radiological evidence of hiatus hernia, and with or without heartburn. In the group without heartburn the mean pressure was 20.4 mm Hg whilst in that with heartburn it was 3.0 mm Hg. These two values are significantly different, and there was a total separation of sphincter pressures between the two groups. Benz *et al.* (1972) studies 21 asymptomatic subjects and 29 patients with heartburn. In the heartburn group 13 patients had a hiatus hernia, and in 24 patients the pressure was below 9.5 mm Hg (mean of the highest end-expiratory and highest end-inspiratory pressure less mean pressure in the stomach). In the control group only four had a pressure below 9.5 mm Hg. Butterfield *et al.* (1972) investigated 14 patients without and 13 patients with heartburn. The mean resting pressures were not found to be significantly different.

As will be seen from this review, the results are far from being concordant. One extreme is represented by materials with different means and total separation between the groups. The opposite extreme is represented by materials, in which there is no difference between means. Nevertheless, the conclusion of most studies is the same as that of the present study, viz. that mean pressure is significantly lower in patients with heartburn, but that there is an appreciable overlapping between the two distributions. Part of the explanation of this discrepancy between the results is to be found in difference in the composition of the materials, but the frequent overlapping between patients and normal subjects is primarily due to the fact that pressures were recorded in the resting state. Sphincter pressure is not a fixed value but varies in relation to changes in intraabdominal pressure, in relation to food intake, just as it may probably change spontaneously. The influence of these factors on sphincter pressure will be dealt with in the following.

It is a clinical experience that heartburn is elicited particularly in relation to procedures which increase the intraabdominal pressure. The normal gastroesophageal sphincter will respond to a rise in intraabdominal pressure with an increase in pressure that is greater than the rise in intragastric pressure and thereby maintain an effective barrier against reflux. Systematic studies of this mechanism were initiated by Lind, Warrian, and Wankling (1966) who investigated the reaction of the normal resting sphincter pressure to an increase in intraabdominal pressure, induced by means of a pneumatic

cuff. During application of 50 mm Hg compression the mean increase in intragastric pressure was 12.8 cm of water and significantly lesser than the mean increase in sphincter pressure of 19.2 cm of water. This excess reaction in the sphincter pressure of normal subjects has been reproduced several times by other investigators (Cohen and Harris, 1969; Hookman and Fleischer, 1969; Cohen and Lipshutz, 1970; Heitmann and Möller, 1970; Cohen and Harris, 1971; Butterfield *et al.* 1972; Dodds, Hogan, Reid, Stewart, Arndorfer, and Malloy, 1972). Cohen and Harris (1969) demonstrated a correlation between resting sphincter pressure and the increase in pressure. Their material consisted of patients and normal subjects, and resting pressures ranged from 2 to over 40 mm Hg. They found an excellent linear correlation between resting pressure and the degree to which sphincter pressure increased as intragastric pressure rose. For resting pressures below 8 mm Hg the ratio of increase in sphincter pressure to rise in intragastric pressure was 1:1, whilst for resting pressure of 35 to 40 mm Hg the ratio was 4:1. This is in agreement with the results of studies, in which the reaction in normal subjects was compared with that in patients with heartburn or a positive acid perfusion test. Hookman and Fleischer (1969) investigated the sphincter reaction to increased intra-abdominal pressure in ten patients with a negative and ten with a positive acid perfusion test. In the negative group the mean sphincter pressure was 20 mm Hg against 10 mm Hg in the positive group. At 30 mm Hg abdominal pressure the sphincter pressure in the negative group rose to 60 mm Hg, and in the positive group to 20 mm Hg. At 60 mm Hg abdominal pressure the corresponding figures were 70 and 30 mm Hg. Cohen and Harris (1971) recorded the resting pressure and the reaction to increased intraabdominal pressure in 38 subjects without radiological evidence of hiatus hernia. Twenty-five were asymptomatic and 13 had heartburn. In the control group mean resting pressure was 20.4 mm Hg against 3.0 mm Hg in the group with heartburn. In patients without heartburn an increase in intraabdominal pressure was followed by a rise in sphincter pressure that always exceeded the increase in intragastric pressure, whilst in patients with heartburn the increase in sphincter pressure was always exceeded by the rise in intragastric pressure. Butterfield *et al.* (1972) studied 14 patients without and 13 patients with heartburn. The mean resting pressure was the same in the two groups. With 80 mm Hg abdominal compression the mean increase in intragastric pressure was the same in the two groups but the rise in sphincter pressure was greater in the asymptomatic group.

These results suggest that patients with a low resting pressure are predisposed to reflux on two points. Firstly, in the resting state the resistance against passage from the stomach into the esophagus will be reduced. Secondly, strain causing a rise in intragastric pressure will not elicit an increase in resistance of the same magnitude as in normal subjects. On the evidence of

the results of the last mentioned report there is reason to believe that not only the resting pressure but also other, still unknown, factors are essential to the reaction of the sphincter in patients with heartburn.

Experience has shown that food intake, and particularly the intake of certain articles of food, is another factor which may produce heartburn. Nebel and Castell (1972a) and Nebel and Castell (1973) studied the effect of various foods on resting sphincter pressure. Ingestion of ground beef increased sphincter pressure. After ingestion of a corn oil meal there was a fall in mean pressure of 7.8 mm Hg, equalling a decrease of 35 per cent. When the corn oil was installed directly into the duodenum the fall in mean pressure was 17.0 mm Hg, equalling a decrease of 62 per cent. In addition, it was demonstrated that corn oil not only inhibits the resting pressure but also reduces the increase in sphincter pressure which is elicited by exogenous and endogenous gastrin. It is unclarified whether the effect is transmitted via a hormone from the duodenum, or whether intraduodenal fat elicits a reflectory reduction in pressure. As regards the relationship between certain articles of food and heartburn, it is worth mentioning that Dennish and Castell (1972) demonstrated that intragastric installation of caffeine sodium benzoate results in a fall in mean pressure.

Beyond these induced variations in sphincter pressure, spontaneous variations are likely to occur. This cannot be directly documented as longterm pressure recordings have not been made but, from the results published by Patrick (1970) there is strong evidence that this is the case. He conducted a study in which intraoesophageal pH was measured continuously over a period of 12 to 24 hr. The study was carried out without any artificial increase in intragastric pH, and the electrode was positioned 5 cm above the hiatus. His material consisted of 49 patients with or without heartburn. The results showed that reflux occurs periodically both in patients with and in those without heartburn. At night, reflux was more frequent in the patients with heartburn. These results have later been reproduced by Stanciu and Bennet (1973a).

Induced and spontaneous variations in sphincter pressure are the principal reasons why, neither in the present nor in several previous materials it has been possible to make a total separation between, on one hand, patients with heartburn and, on the other, patients without heartburn and normal subjects. The symptom heartburn is based solely on clinical characteristics and is most pronounced in association with strain known to affect the sphincter pressure. This symptom has been related to resting pressure, which gives only an instantaneous picture of the pressure conditions. Such a comparison ignores the fact that the sphincter is a dynamic structure, the pressure of which changes under the influence of different factors. Another reason is that the sensitivity to acid varies both from individual to individual and in the single

individual. Benz *et al.* (1972) reported three asymptomatic subjects, in whom perfusion of the esophagus with acid resulted in the occurrence of heartburn and substernal discomfort. These subjects had a normal resting pressure, and it was not possible by use of the pH probe to demonstrate reflux of acid. The authors concluded that the esophagus of the three subjects was sensitive to acid, but because the barrier to reflux was competent, the esophagus was not exposed to acid and therefore heartburn did not occur. In the same material mention is made of seven patients, who were studied after intensive antacid treatment for severe heartburn. At the time of the study they were asymptomatic, and the acid perfusion tests were negative. Further studies revealed that they had a very low resting pressure, and they still refluxed acid as determined by the pH test. These patients did not have an effective barrier against reflux but the esophagus was not, for the moment, sensitive to acid. In relation to these results it should be mentioned that Booth, Kemmerer, and Skinner (1968) and Skinner and Booth (1970) demonstrated that the ability of the distal esophagus to clear acid is dependent on the peristaltic activity. For these investigations they used a pH electrode placed 5 cm above the upper end of the sphincter, and 15 ml 0.1 N hydrochloric acid was injected through a catheter with a side-hole 10 cm above the electrode. They observed the number of swallows required to raise the pH of the distal esophagus to 6.0. All the normal subjects achieved this with from four to ten swallows. Patients with moderate to severe heartburn and esophagitis showed prolonged clearing, and swallowing was less effective in raising the pH. It was concluded that efficient peristalsis initiated by swallowing is necessary for normal clearing. This conclusion has been supported by later published results (Stanciu and Bennett, 1973; Stanciu and Bennet, 1973a).

In the reflections on the pathophysiology of a low sphincter pressure it should be borne in mind that by means of drugs it is possible to change not only the pressure but also the response to an intraabdominal increase in pressure. In their previously mentioned work Cohen and Harris (1969) state that when resting sphincter pressure was pharmacologically changed, the ratio of increase in sphincter pressure to increase in intragastric pressure did not remain at its original value but changed to a value for the new baseline. Hookman and Fleischer (1969) investigated the effect of prostigmin on resting sphincter pressure and the reaction to increase in intraabdominal pressure. The material consisted of normal subjects and patients with a positive acid perfusion test. The pressure was increased by means of an abdominal pressure cuff, inflated to 30 mm Hg. Before prostigmin the resting pressure in the patient group was 10 mm Hg, and the increase in pressure on abdominal compression was 10 mm Hg. The corresponding figures after prostigmin were 15 and 15 mm Hg. It was also demonstrated that atropine lowered resting pres-

sure as well as the increase on abdominal compression in normals and patients with positive acid perfusion test. Cohen and Lipshutz (1970) studied the sphincter response before and after intravenous injection of atropine sulphate in doses ranging from 0.01 to 0.02 mg per kg. The mean resting sphincter pressure declined from 22 to 9 mm Hg. After atropine the adaptive increases in pressure with induced changes in intraabdominal pressure were significantly reduced.

These results demonstrates that if changes in sphincter pressure are induced pharmacologically the response to an intraabdominal rise in pressure will be dependent on the actual pressure and independent of the previous baseline. In patients with a low pressure and a weak response to increase in intraabdominal pressure a normal resting pressure may be induced pharmacologically, and the response to an increased pressure will then quantitatively be the same as in normal subjects. This means that the pathophysiology of a low resting sphincter pressure cannot be ascribed to a primary defect of the sphincter muscle but must be secondary to a reduced endogenous stimulation.

The endogenous factor or factors that condition a low pressure are unknown. The physiological control of sphincter pressure involves neurogenic factors, alpha- and beta-adrenergic and cholinergic receptors, and the hormones gastrin and secretin. In the case of most of these factors it is not technically possible to record their activity, and the theroretically possible causes of a low pressure are numerous. Serum gastrin may be determined by immunoassay, but results from materials comparable to the present one have not been published. On the evidence of the results reported by Rosenberg and Harris (1971) it may be supposed that a low serum gastrin level is one of the pathophysiological factors. These authors constructed dose-response curves for the action of pentagastrin on sphincter pressure and acid secretion. Pentagastrin was administered subcutaneously, and the material consisted of normal subjects and patients with "clinical gastroesophageal reflux". The normals showed a peak rise in pressure of 270 per cent at a pentagastrin dose of 0.5 μ g per kg. Both shape and percentage increase of the incompetent sphincter dose-response curve was the same as normal, but twice as much pentagastrin was required for peak response. The gastric acid dose-response curve of normals showed a peak response at 2.5 μ g per kg. A dose-response curve of the same shape was observed in the patient group, but acid secretion was only about half normal at each dose. It was concluded that incompetent sphincter is not due to a primary defect of the sphincter muscle but secondary to decreased stimulation of endogenous gastrin. This conclusion may be correct, but the same results are to be expected in cases with low cholinergic activity. Lipshutz, Gaskins, and Lukash (1973) studied sphincter function in 20 patients with reflux and 20 matched controls. The percent change in pressure in response to exogenous stimulation by bethanechol chlo-

ride and pentagastrin was the same in both groups. The percent change in pressure in response to endogenous stimulation by gastric deacidification or gastric installation of glycine was significantly lower in the reflux group. These results demonstrated that the pathophysiology of sphincter incompetence may be related to a decrease in the release of endogenous gastrin.

Abnormally high sphincter pressure – hypertensive sphincter – was first described by Code, Schlegel, Kelly, Olsen, and Ellis (1960) from the Mayo Clinic. They used balloon-technique and non-perfused catheters, and pressures higher than 140 cm water were defined as hypertensive sphincter. Their material consisted of 45 patients equally distributed on both sexes. No mention was made of how many cases of hiatus hernia there was. The most frequent symptom was pain, and about half the patients had dysphagia. Likewise, about half the patients had insufficient relaxation of the sphincter on swallowing, and 21 out of the 45 patients displayed manometric characteristics of a spastic esophagus. The hypertensive sphincter has later been dealt with in several publications from the Mayo Clinic, and they confirm in all essentials the first description of the clinical and manometric characteristics (Ellis, Code, and Olsen, 1960; Code *et al.* 1962; Schmidt *et al.* 1962; Ellis, Olsen, Schlegel, and Code, 1964). There is only a single material, in which hypertensive sphincter has been defined by means of perfused catheters (Heitmann, 1970). In this material the lowest normal pressure was 3 and the highest 18 mm Hg. The material consisted of nine patients, all of whom had a pressure that was higher than 20 mm Hg. All of them had hiatus hernia and the manometric characteristics of a spastic esophagus. Pain and dysphagia were prominent symptoms. In the present material 27 patients had a pressure above the upper limit of normal. Fourteen had dysphagia, in four of whom the curve pattern was normal, whilst the remaining ten patients had one or more abnormalities by way of spastic esophagus, or insufficient relaxation of the sphincter on swallowing.

In most cases the dysphagia may be ascribed to abnormalities in the corpus of the esophagus on swallowing, but the cause of the pain is only clarified in part. In the cases, in which hypertensive sphincter occurs concurrently with a spastic esophagus, the pain may solely or partly be ascribed to the contraction of the corpus of the esophagus. This view is supported by the fact that in some cases it is possible by injection of cholinergic agents to elicit spastic contraction of the corpus as well as pain (Fleshler, 1967; Kramer, Fleshler, McNally, and Harris, 1967; Kramer, Harris, and Donaldson, 1967; Heitmann, 1970).

In cases of hypertensive sphincter without spastic esophagus the cause of pain remains obscure, and this problem is closely related to the pathophysiology. There are two possibilities: One is that the hypertensive sphincter is

a disease entity *per se* and thus the cause of the clinical picture. The other is that the hypertensive sphincter is secondary to pathophysiological conditions involving other organs and therefore only partly responsible for the symptoms. The first possibility is supported by Ellis *et al.* (1964), who performed myotomy in the sphincter area of six patients with hypertensive sphincter without spastic esophagus. The preoperative symptomatology was characterised by pain in two cases, by pain and dysphagia in three, and by dysphagia in one. Results were stated as excellent or good in four, fair in one, and poor in one. This means that a hypertensive sphincter must, in some cases, be a disease entity *per se* presenting symptoms. Research of recent years has increased the number of hormonal and neurogenic factors that are known to affect sphincter pressure, and there are now more theoretical possibilities of hypertensive sphincter being part of a larger pathophysiological entity. These possibilities will be discussed in the chapter dealing with sphincter pressure in relation to spontaneously occurring or operatively induced organic changes of the upper abdomen.

In the present material the mean sphincter pressure was higher in patients with dysphagia than in normal subjects. For the whole of the material and for the group of patients with hypertensive sphincter the frequency of abnormalities in relation to swallowing was higher in patients with dysphagia than in those without. In this connection it should be borne in mind that the material does not include patients with achalasia or organic changes in the esophagus. The abnormalities were in the nature of insufficient relaxation of the sphincter, spastic esophagus or a combination of both. Still, there are also patients with dysphagia but without abnormalities, and vice versa.

There are probably several reasons why the above mentioned separation is not total. One of the most essential is that the method employed does not give adequate information about the transport mechanism in the esophagus. Sufficient relaxation signifies only that the activity of the muscular component of the gastroesophageal barrier is suspended. A free passage for the bolus requires not only obliteration of the pressure gradient but also distension of the gastroesophageal region. Possible impediments, for example wall rigidity or external compression, can cause dysphagia, and they may be present without the manometric investigation recording abnormalities.

Furthermore, it should be mentioned that the flow rate used in the present study does not allow a reliable recording of the amplitude of the peristaltic contractions of the corpus. There is reason to believe that insufficient relaxation can be compensated for if the amplitude of the peristaltic contractions is sufficiently high; the method used is unsuitable to elucidate this matter, however. Likewise it is unsuitable to get information about the transport mechanism in spastic esophagus. Simultaneous and repetitive con-

tractions with the same amplitudes on different levels are incompatible with normal transport of the bolus, but the transport mechanism can be expected to be normal – and therefore not accompanied by dysphagia – in the cases in which the pressure maximum of the repetitive complexes is propagating.

CHAPTER VI

Gastroesophageal sphincter pressure in patients with hiatus hernia

Introduction

In cases in which no other organic changes can be demonstrated, a hiatus hernia will usually be accepted as being the cause of symptoms from the upper abdomen. On the other hand, the clinical picture may be so varied and have so many components that in several cases there is reason to suppose that they cannot all be ascribed to the hernia. This view is supported by the fact that most surgical materials include cases of radiologically verified reposition but with unchanged symptomatology. Therefore it is an absolute condition of a relevant and differentiated treatment to try to clarify in each individual case whether the complex of symptoms can be accepted as being caused by a hiatus hernia. Such a clarification will call for a diagnostic programme including radiological examination, acid secretory test, manometric study of the sphincter pressure and the motility in the corpus of the esophagus, acid perfusion test, and a continuous recording over a longer period of the pH in the lower part of the esophagus.

The purpose of the present study has not been to assess the value of the various methods in differentiating between different types of hiatus hernia, but the attention has been confined to a survey of the clinical picture and the results of the manometric studies.

Material

The criteria for acceptance in the material are based on the results of the diagnostic examinations. All patients fulfill the following conditions:

1. Radiological evidence of hiatus hernia of the sliding type
2. No other demonstrable organic cause of the symptoms than the hernia
3. No previous operations in the upper abdomen

In the period December, 1970, to January, 1973, manometric studies were made of 83 patients, fulfilling the above criteria. Recordings were technically unsatisfactory in ten patients, and the processed material thus consists

of 73 patients. There were 40 women and 33 men, who varied in age from 41 to 85 years, with a mean age of 61 years.

The distribution of the various symptoms is shown in table I, and table II lists the diagnostic programme.

Thirty-four patients were later subjected surgical treatment of the hernia.

Method

The *manometric studies* were carried out as described in chapter IV.

Results

Fig. 1 lists each sphincter pressure in the total material, in patients with heartburn or heartburn and pain (group A), in patients with dysphagia or dysphagia and pain (group B), and in patients with heartburn and dysphagia or pain, heartburn, and dysphagia (group C). The various characteristics of sphincter pressure in the corresponding groups are listed in tabel III. Thirty-four patients had a pressure below the lower limit of normal, and of these 26 had heartburn. The pressure was within the normal area in 28 patients, 13 of whom had heartburn. None of the 11 patients with a pressure above the upper limit of normal had heartburn. Mean pressure in group A

Symptoms	No. of Patients
Without symptoms	3
Pain	24
Heartburn	10
Dysphagia	1
Pain and heartburn	14
Pain and dysphagia	6
Heartburn and dysphagia	1
Pain, heartburn and dysphagia	14
Total	73

Table VI-I. The distribution of the various symptoms in the total material.

Diagnostic examinations	No. of patients
X-ray, esophagus, stomach, and duodenum	73
X-ray, biliary tract	24
X-ray, colon	19
Esophagoscopy	38
Gastroscopy	25

Table VI-II. The diagnostic programme in the total material.

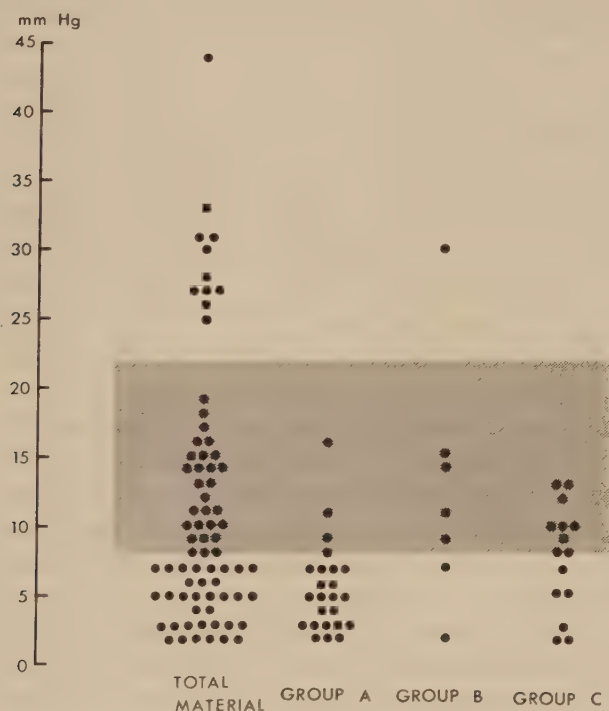


Fig. VI-1. Sphincter pressures in patients with hiatus hernia. Subgrouping according to criteria mentioned in the text.

is lower than in the normal material ($0.01 > p_{MW}$). In group B, mean pressure is not significantly different from the normal mean. Mean pressure in group C is lower than in the normal material ($0.01 > p_{MW}$). The three pa-

	n	Mean	Range	P_{χ^2}
Total material	73	11	2-44	0.005 > p > 0.001
Group A	24	6	2-16	—
Group B	7	13	2-30	—
Group C	15	8	2-13	—

Table VI-III. Characteristics of sphincter pressure in patients with hiatus hernia. Subgrouping according to criteria mentioned in the text.

tients without symptoms had a pressure of 14, 15, and 18 mm Hg, respectively.

Out of the 22 patients with dysphagia three displayed abnormalities in the sphincter or the corpus of the esophagus on swallowing. This was also the case in five of the remaining 51 patients.

Discussion

The results of the present study demonstrate that patients with hiatus hernia of the sliding type constitute a heterogeneous group. The distribution of sphincter pressure is not normal but characterized by the occurrence of a great number of cases with low pressures and a smaller group with high pressures. In 28 out of the 73 patients the pressure was of the same magnitude as in normal subjects, in 34 it was lower than, and in 11 it was higher than the lower and upper limit of normal, respectively. Accordingly, the disease had two characteristics in 45 cases, — the presence of a hiatus hernia, and an abnormal sphincter pressure.

However, it has to be emphasized that the diagnostic programme does not allow any conclusions about the cause of symptoms in each case, and it is reasonable to assume that diseases of different pathophysiology are represented. For that reason, the material must be regarded as heterogeneous and inapplicable for calculations as a whole.

The relationship between dysphagia and abnormalities in sphincter-re-

laxation and motility was discussed in chapter V. In the present material another cause of dysphagia is added, – the presence of a hernia. This also appear from the fact that the frequency of dysphagia far exceeds the frequency of disturbances in sphincter-relaxation and motility.

As was the case in the group of patients with dyspepsia without organic cause, the patients with heartburn had a mean sphincter pressure that is lower than in normal subjects. This apply to the group of patients with heartburn or heartburn and pain, as well as to the group of patients with heartburn and dysphagia or pain, heartburn, and dysphagia. However, also in the case of patients with hiatus hernia there is appreciable overlapping between the distributions. The possible causes of this overlapping have been discussed in chapter V, and as the same argumentation applies to the present material this discussion will not be repeated here.

The results are well in keeping with those reported by Heitmann (1969). He made a comparative study of sphincter pressures in 30 normal subjects and 70 patients with hiatus hernia. In the normal subjects mean pressure was 11.1 mm Hg, with the lowest being 3 and the highest 18 mm Hg. Patients with reflux had a mean pressure that was lower than in normal subjects, and lower than in patients with hernia but without reflux. There was, however, a considerable overlapping between the groups. Out of the 29 patients with reflux 26 had intense heartburn. Of the 70 patients, seven had a hypertensive sphincter. Cohen and Harris (1971) also made comparative studies of sphincter pressures in normal subjects and patients with hiatus hernia. Mean pressure was 20.4 mm Hg for the normals and 19.6 mm Hg for the patients with hernia but without heartburn. Patients with hiatus hernia and heartburn had a mean pressure of 3.8 mm Hg. There was a total separation between, on one side, patients with hiatus hernia and heartburn and, on the other side, normal subjects and patients with hiatus hernia but without heartburn. Haddad (1970) studied the relationship between sphincter pressure and the results of intraesophageal pH recordings. The investigations were carried out after introduction of 300 ml 0.1 n hydrochloric acid into the stomach. Of a total of 28 cases of hiatus hernia 13 demonstrated free or spontaneous reflux, eight demonstrated reflux only with straining manœuvres, and the remaining seven did not show reflux. Reflux was associated with pressures that were lower than those in the control group, and patients with the most marked degree of reflux had the lowest sphincter pressures.

It has formerly been the generally accepted view that dislocation of the sphincter to the thorax was accompanied by a change in the response pattern and a reduction in the capacity of the sphincter to prevent reflux. Studies carried out in recent years have demonstrated, however, that the charac-

teristics of the sphincter are independent of the location and dependent only on resting pressure. Cohen and Harris (1970) studied the relationship of sphincter pressure to sphincter strength. The strength was defined as the force in grammes required to pull a Teflon ball from the stomach, through the sphincter and into the esophagus. In 25 normal subjects they found an excellent correlation between pressure and strength, both at rest and during increased intraabdominal pressure. They also studied 13 patients with large asymptomatic sliding hiatus hernia and found the same relationship of pressure to strength. The slope of the regression line and the correlation was the same as for normal subjects. They concluded that the pressure recorded by constant infusion technique is a valid index of strength independent of the location of the sphincter. Cohen and Harris (1971) demonstrated that the response of the sphincter to intraabdominal increase in pressure is not influenced by a hiatus hernia. The ratio of increase in sphincter pressure to increase in intragastric pressure is the same in patients with hernia as in normal subjects.

The two last mentioned studies demonstrate that the dislocated sphincter has characteristics which, qualitatively and quantitatively, do not differ from those of the normally located sphincter. At a certain pressure the resistance against reflux will be the same irrespective of the location of the sphincter, and the response to a rise in intraabdominal pressure will be dependent on the actual pressure and independent of the hernia. Hence it is clear that the distribution of sphincter pressures in the present and previously reported materials cannot be directly applied to the distribution in a total population with hiatus hernia. The materials are selected and composed of patients with symptoms of an intensity necessitating a closer investigation into the cause. An essential part of the explanation of the great number of cases of low pressure must be that it is the low pressure *per se* and not the presence of the hernia which conditions the development of symptoms. The low resistance against passage from the stomach to the esophagus allows reflux, and the resulting irritation of the lower part of the esophagus gives rise to symptoms.

It is not yet clarified whether the pathophysiological factors that condition the development of a hiatus hernia also influence the sphincter pressure. This problem raises two questions: – does the sphincter alone create the high pressure zone, or do the paraesophageal structures contribute? and – is dislocation of the sphincter *per se* accompanied by changes in sphincter pressure? As to the first question there are experimental indications that the paraesophageal structures make only a minor contribution to the high pressure zone. Vandertoll, Ellis, Schlegel, and Code (1966) investigated the effect of circular myomectomy of the sphincter area on pressure. These studies

were made using non-perfused catheters. It was found that myomectomy abolished the high pressure zone. These results were later reproduced by Siewert, Jennewein, Waldeck, and Peiper (1973a). They also used dogs but recorded the pressure using perfused catheters. A circular myomectomy was followed by a reduction in pressure to about 4 mm Hg. In the light of these studies it could be expected that a dislocation of the sphincter would not *per se* be followed by a notable fall in pressure. There is only a single publication reporting a study of this problem by means of perfused catheters (Lind *et al.* 1969). These authors studied sphincter pressure before and after displacement of the sphincter into the thorax of dogs. The surgical procedure involved circumferential division of the phrenicoesophageal ligament. Pressures were found to be unchanged after this procedure, and it was concluded, that the anatomical location of the sphincter and the paraesophageal structures do not contribute to the high pressure zone. Likewise it was found that the response of the sphincter to an increase in intraabdominal pressure was similar to that observed before surgery.

The answer to the above two questions is that experiments seem to show that the high pressure zone may chiefly be related to the sphincter, and that a surgically constructed hernia is not followed by a fall in pressure. It should be borne in mind, however, that the surgical construction involves destruction of structures which are intact in cases of spontaneously occurring hernia in man. The experiments are of great interest for the studies of the physiology and pathophysiology of the sphincter but ignore the fact that the pathophysiological factors that are responsible for the development of a hernia are not present. Therefore the two situations can hardly be compared, and it is possible that the pathophysiological factors contribute not only to the development of a hernia but also to changes in the sphincter pressure.

On the evidence of the animal experiments mentioned it may seem paradoxical that several investigators have demonstrated an increase in sphincter pressure after surgical reposition of hernias in man. Lind, Burns, and MacDougall (1965) studied the effect of a modified Belsey technique on sphincter pressure in 16 patients with a hernia. Pressures were recorded with non-perfused catheters, and the operation induced a significant increase in mean sphincter pressure from 22.5 to 33.4 cm water. This result has later been reproduced by other authors using perfused catheters. Skinner and Booth (1970) studies 14 patients before and after either a Belsey Mark IV procedure or a Nissen fundoplication operation. The postoperative mean pressure was 5.8 mm Hg higher than the preoperative mean. Moran, Pihl, Norton, and Rheinlander (1971) studied the effect of herniotomy *a. m.* Belsey in 14 patients. The result was a significant rise in pressure, from 9 to 15 mm Hg. The latest work is by Csendes and Larrain (1972). They

studied sphincter pressure in 29 patients before and after posterior gastropexy a. m. Hill. The operation induced a significant rise in mean pressure from 3.48 to 12.45 mm Hg.

Animal experiments, on one hand, demonstrate that dislocation of the sphincter to the thorax is not followed by a fall in pressure whilst human studies, on the other hand, clearly show that surgical reposition results in a rise in mean pressure. Siewert *et al.* (1973a) have given an explanation of this discrepancy. Using perfused catheters they studied in dogs the effect of fundoplication partly on the normal sphincter, partly on the sphincter after different operative interventions. In cases of intact sphincter fundoplication was followed by a rise in pressure to 50 to 60 mm Hg. Injection of pentagastrin led to a further rise, and after injection of glucagon the pressure dropped to about 10 mm Hg. Circular myomectomy of the sphincter area was followed by a marked fall in pressure, and there was no response to pentagastrin or glucagon. Fundoplication after myomectomy resulted in an increase in pressure, and another increase occurred after injection of pentagastrin and carbaminoylecholine, respectively.

In brief, this series of studies demonstrate that by means of a fundus cuff it is possible to create a high pressure zone between the stomach and the esophagus. Following injection of pentagastrin, glucagon and cholinergic drugs the pressure gradient has the same response pattern as the normal gastroesophageal sphincter. The results are supported by the fact that *in-vitro* it has been possible to demonstrate that muscle from the anterior wall of the fundus next to the cardia responded to pentagastrin with contraction. This elegant series of studies is closed by an investigation of the effect of fundoplication on sphincter pressure in patients with incompetent sphincter. The pressure established by the cuff raised the insufficient pressure to a mean of 17.3 mm Hg in 15 patients. All patients had normal relaxation on swallowing and the response to pentagastrin and glucagon was qualitatively as expected, while quantitatively it was weaker than in normal subjects with the same pressure.

As will be seen from this review of the most important human and animal studies, research of recent years has in essential respects contributed to a better understanding of the function of the sphincter in patients with hiatus hernia. The presence of a hernia is not *per se* a decisive factor. The concurrently existing changes in sphincter pressure are today held to be the direct or indirect cause of the symptoms. A low pressure renders reflux possible and may therefore be regarded as the indirect cause of the symptoms that are elicited when gastric contents make contact with the esophageal mucosa. In these cases resting pressure should be taken as a guidance and supplementary diagnostic examinations are required to clarify the causal relation.

In cases of hypertensive sphincter the high pressure is accepted as being solely or partly responsible for the symptoms, and in such cases manometric measurements are decisive for the diagnosis. By means of the diagnostic equipment available at present it will be possible to divide a heterogenous material of hiatus hernia into smaller and more homogenous groups. Each of these groups will have special pathophysiological characteristics, and it is these differences that necessitate a differentiated therapeutic programme.

CHAPTER VII

Gastroesophageal sphincter pressure in patients with gastric or duodenal ulcer

Introduction

In recent years there have been numerous detailed reports of gastric acid secretion in patients with gastric or duodenal ulcers, and the results have lent support to the various pathogenetic theories of the development of ulcers. The actual gastric acid secretion is principally determined by three factors, serum gastrin, total parietal cell mass, and the vagal tone in parietal cells. Serum gastrin, vagal tone, and acidity of the gastric contents are essential factors in the regulation of sphincter pressure, and I was therefore interested in investigating whether the pathophysiological conditions associated with ulcers would involve changes in sphincter pressure.

Material

During the period December, 1970, to January, 1973, manometric studies were made in 110 patients with an ulcer. Of these five had to be excluded for technical reasons, and thus the series made a total of 105 patients, who were grouped as follows, according to location of the ulcer:

Uncomplicated duodenal ulcer. This group comprised 56 patients, nine women and 47 men. Only patients with a radiologically verified niche in the duodenal bulb were included. Ages varied from 20 to 78, mean age 49 years. The diagnosis was verified surgically in 24 cases.

Uncomplicated prepyloric ulcer. This group comprised 12 patients, six women and six men. The diagnosis was verified by surgery in four cases and by radiological examination and gastroscopy in the remaining cases. Ages ranged from 20 to 68, mean age 48 years.

Uncomplicated gastric ulcer. This group comprised 14 patients, six women and eight men. The diagnosis was verified surgically in 12 cases, and by radiological examination and gastroscopy in the remaining cases. Ages varied from 28 to 72, mean age 53 years.

Complicated ulcers. This group comprised 23 patients and included cases of two or more ulcers of different location, cases complicated by gallstones or pyloric stenosis, and previously cholecystectomized cases. Since there is no reason to suppose that this group constitute a pathophysiological entity it will be given no further mention.

Method

The *manometric studies* were carried out as described in chapter IV.

The *acid secretory tests* were performed as follows:

The patient fasted for 12 hr prior to the examination, which took place in the morning. A radiopaque nasogastric tube was introduced, and its position controlled by screening. The basal secretion was collected over a period of 1 hr, and subsequently the stomach was stimulated with pentagastrin, 6 μg per kg, given subcutaneously. By constant mechanical suction the gastric secretion was collected during four 15-min periods. The basal secretion and the secretion from the four 15-min collections were measured for volume, pH, and acid concentration by titrating with 0.1 n sodium hydroxide to pH 3.5. For all collected portions the acidity was then calculated in m-equiv H^+ per l, and the secretion in m-equiv H^+ .

As variables for gastric acid secretion were used basal acid secretion and peak acid secretion. Both values were expressed in m-equiv H^+ per hr, and peak acid secretion was calculated to be the sum of the largest consecutive 15-min collections multiplied by two.

Results

Fig. 1 shows the sphincter pressure recorded in each individual patient. Tables I, II, and III show characteristics of sphincter pressure and acid secretion in the patients with duodenal, prepyloric, and gastric ulcer, respectively. The mean sphincter pressure is lower in the patients with duodenal ulcer than in the normal material ($0.001 > p_{\text{atu}}$, $0.001 > p_{\text{MW}}$). There is no significant difference between the mean pressure for the normal material and the two other ulcer groups.

In the duodenal ulcer group 26 patients did not suffer from heartburn, whilst this was commonly occurring in the remaining 30. These two groups were compared, and the characteristics of both appear in table IV. The difference between means is significant ($0.01 > p_{\text{MW}}$) but, then there was a considerable overlapping in the two groups.

In all three ulcer groups an analysis was made of the relationship between sphincter pressure and the basal acid secretion and the peak acid secretion, respectively. The relationships are shown in fig. 2–7. Neither the coefficient of correlation nor the Sperman's coefficients of correlation are significant.

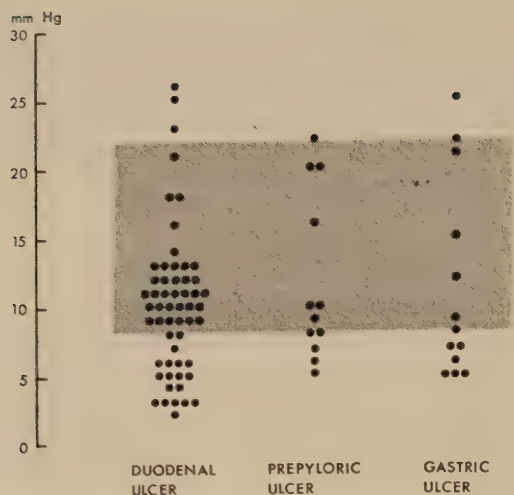


Fig. VII-1. Each individual sphincter pressure in the total material in relation to the normal area (hatched).

	n	Mean	Range	s ²	p χ^2
Sphincter pressure (mm Hg)	56	10	2-26	28.9	0.05)p>0.025
Basal acid secretion (m-equiv/hr)	56	3.1	0.0-13.8	—	0.01)p>0.005
Peak acid secretion (m-equiv/hr)	56	36.8	12.1-72.0	195.9	0.30)p>0.20

Table VII-1. Characteristics of sphincter pressure and acid secretion in patients with duodenal ulcer.

Out of the 105 patients, ten had periodic dysphagia. Among these ten patients, six displayed abnormalities in the sphincter or the corpus of the esophagus on swallowing; four of them presented characteristics similar to those seen in spastic esophagus, and two had insufficient relaxation of the sphincter. Of the remaining 95 patients two had insufficient relaxation of the sphincter.

	n	Mean	Range
Sphincter pressure (mm Hg)	12	12	5–20
Basal acid secretion (m-equiv/hr)	12	2.6	0.0–11.1
Peak acid secretion (m-equiv/hr)	12	29.9	8.8–38.1

Table VII-II. Characteristics of sphincter pressure and acid secretion in patients with prepyloric ulcer.

	n	Mean	Range
Sphincter pressure (mm Hg)	14	12	5–27
Basal acid secretion (m-equiv/hr)	14	0.6	0.0– 2.3
Peak acid secretion (m-equiv/hr)	14	16.7	6.0–31.5

Table VII-III. Characteristics of sphincter pressure and acid secretion in patients with gastric ulcer.

	n	Mean	Range
Duodenal ulcer without heartburn	26	13	3–26
Duodenal ulcer and heartburn	30	8	2–14

Table VII-IV. Characteristics of sphincter pressure (mm Hg) in duodenal ulcer patients with and without heartburn.

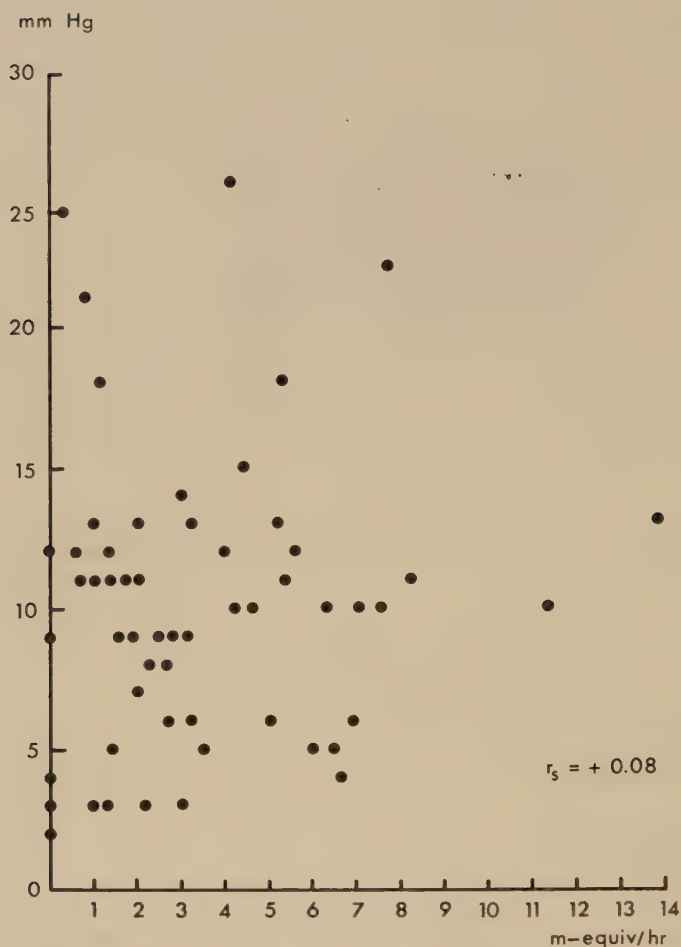


Fig. VII-2. The relationship between basal acid secretion (m-equiv/hr) and sphincter pressure (mm Hg) in patients with duodenal ulcer.

Discussion

In the present study the mean sphincter pressure is lower in the patients with a duodenal ulcer than in the normals, whilst in prepyloric and gastric ulcer it is of the same magnitude as in the normals. In duodenal ulcer patients with heartburn, mean sphincter pressure is lower than in the remaining patients in the same group.

Several investigators have studied the effect of gastric surgery on sphincter pressure, whilst there are only a few reports in which the sphincter pressure in the non-operated ulcerated stomach has been compared to that in healthy subjects. Crispin, McIver, and Lind (1967), using perfused cathe-

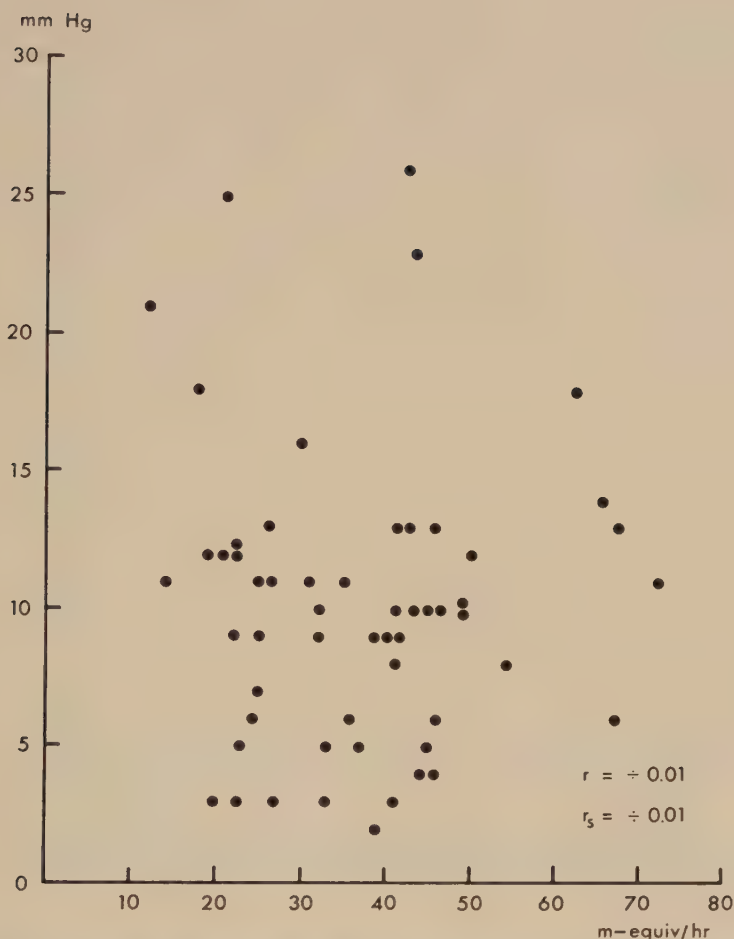


Fig. VII-3. The relationship between peak acid secretion (m-equiv/hr) and sphincter pressure (mm Hg) in patients with duodenal ulcer.

ters, found that the mean sphincter pressure in ten patients with an ulcer was of the same magnitude as that in a group of healthy controls. Location of the ulcers was not stated. Mann and Hardcastle (1968) used non-perfused catheters and found that the mean pressure in nine patients with an ulcer did not differ from that in healthy controls.

The cause of the low sphincter pressure in patients with duodenal ulcer is to be sought for in changes in one or more of the hormonal and neurogenic mechanisms responsible for the maintenance of the resting sphincter pressure. Investigations carried out in recent years have demonstrated that gastrin is one of the essential factors. Exogenous gastrin increases sphincter pressure and this effect can be reproduced by procedures stimulating the re-

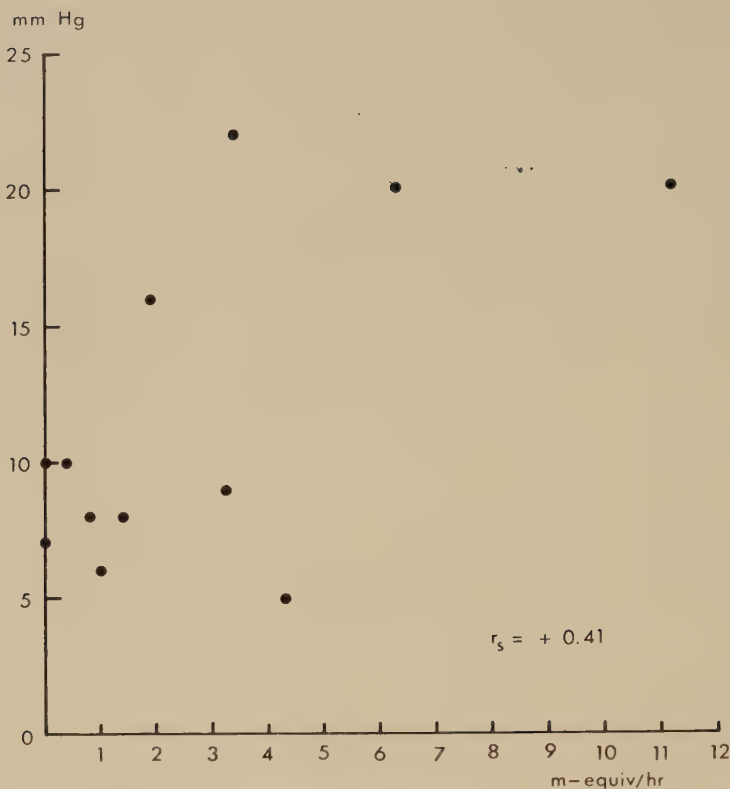


Fig. VII-4. The relationship between basal acid secretion (m-equiv/hr) and sphincter pressure (mm Hg) in patients with prepyloric ulcer.

lease of endogenous gastrin (Giles *et al.* 1969a; Castell and Harris, 1970; Castell and Levine, 1971; Cohen and Lipshutz, 1971). The fact that gastrin contributes to the maintenance of the resting sphincter pressure was demonstrated by Lipshutz *et al.* (1972). They studied the effect of gastrin antiserum upon resting sphincter pressure in opossum. Increasing amounts of antisera produced a graded inhibition in pressure, and the maximal inhibition represented a 80 per cent reduction. They also found that the increase in pressure induced by installation of sodium hydroxide was reduced after gastrin antiserum from a mean of 38.7 to 3.0 mm Hg. These results would suggest that gastrin is not only an essential factor in the maintenance of a normal sphincter pressure but, that it is also active in changes induced by a fall in the acidity of the gastric contents. If changes in serum gastrin are likely to be responsible for the low mean sphincter pressure in duodenal ulcer, one would expect a low mean fasting serum gastrin in duodenal ulcer. It is not fully elucidated, however, whether in duodenal ulcer serum gastrin

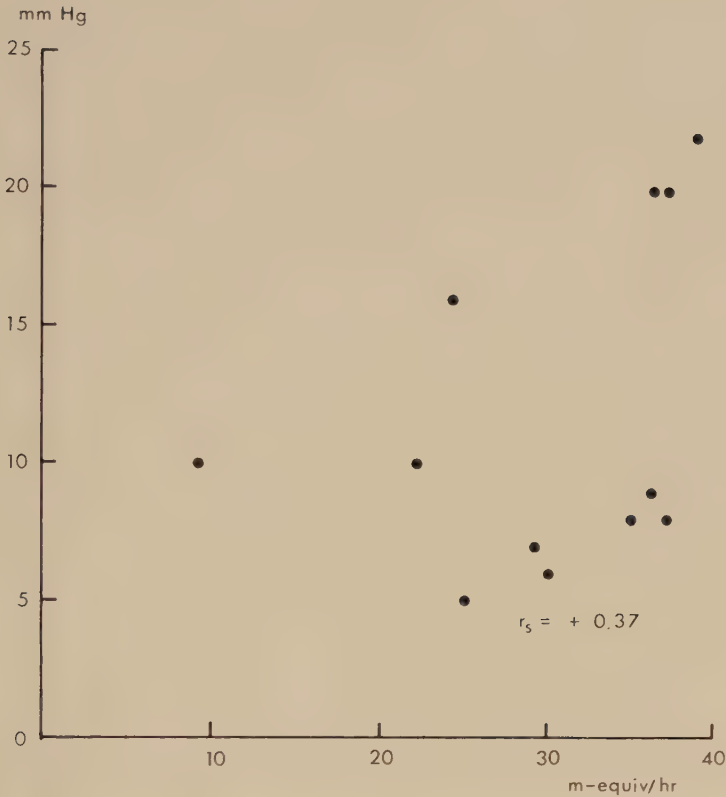


Fig. VII-5. The relationship between peak acid secretion (m-equiv/hr) and sphincter pressure (mm Hg) in patients with prepyloric ulcer.

deviates from normal. A few investigators have found values lower than they found in healthy individuals (Hansky and Cain, 1969; Korman, Soveny, and Hansky, 1971), whilst others found higher values (Byrnes, Young, Chrisholm, and Lazarus, 1970; Berson and Yalow, 1972; Feurle, Ketterer, Becker, and Creutzfeld, 1972). Yet it is the prevailing view that serum gastrin is normal i duodenal ulcer (Trudeau and McGuigan, 1970; Trudeau and McGuigan, 1971; Ganguli and Hunter, 1972; Kaess, Dörner, and Dörner, 1972; Schrumpf and Sand, 1972; Stern and Walsh, 1972; Trudeau and McGuigan, 1972; Stadil and Rehfeld, 1973). The action of gastrin on the sphincter pressure is inhibited competitively by secretin but, both exogenous and endogenous secretin release are without effect on the normal sphincter pressure (Cohen and Lipshutz, 1971). Thus there is no indication that a low serum gastrin should be the cause of the low sphincter pressure in duodenal ulcer, and an increase in serum secretin, if any, is not likely to lower the normal level of sphincter pressure.

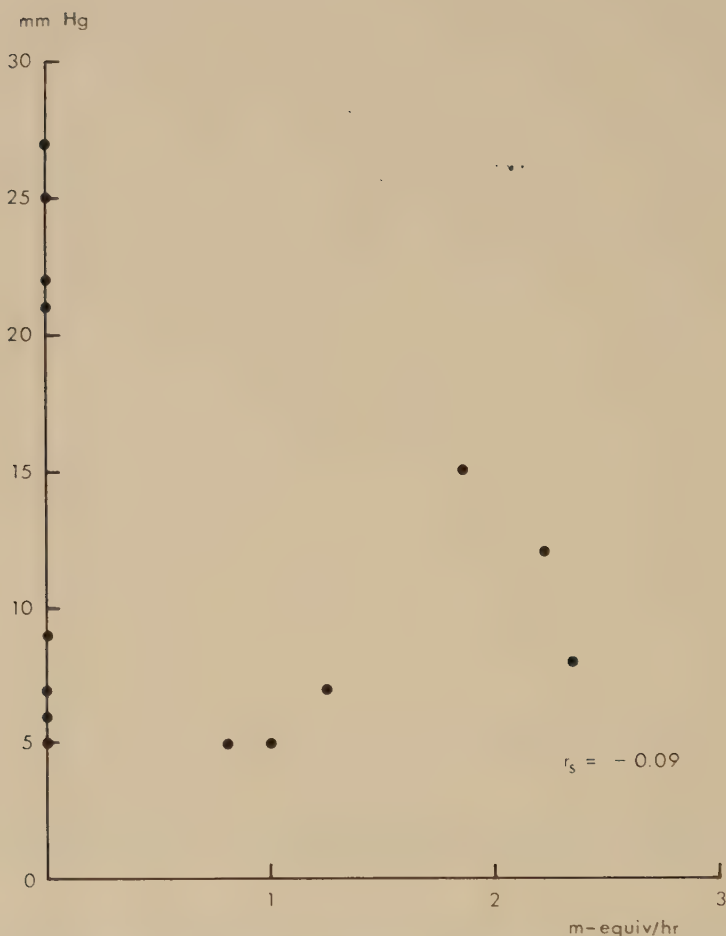


Fig. VII-6. The relationship between basal acid secretion (m-equiv/hr) and sphincter pressure (mm Hg) in patients with gastric ulcer.

It is well-established that in duodenal ulcer the mean basal acid secretion is higher than in healthy subjects, and it has been demonstrated repeatedly that an induced increase in the acidity of the gastric contents will change the sphincter pressure. Intra-gastric installation of acid decreases sphincter pressure, and the decrease is parallel to the increase in acidity (Castell and Harris, 1970; Castell and Levine, 1971; Cohen and Lipshutz, 1971; Cohen *et al.* 1971). This decrease is supposed to be conditioned by an artificially induced reduction in serum gastrin but, measurements taken simultaneously of sphincter pressure and serum gastrin are not available.

Induced changes in the acidity of the gastric contents can additionally also affect the sphincter via neurogenic mechanisms. Several animal experiments

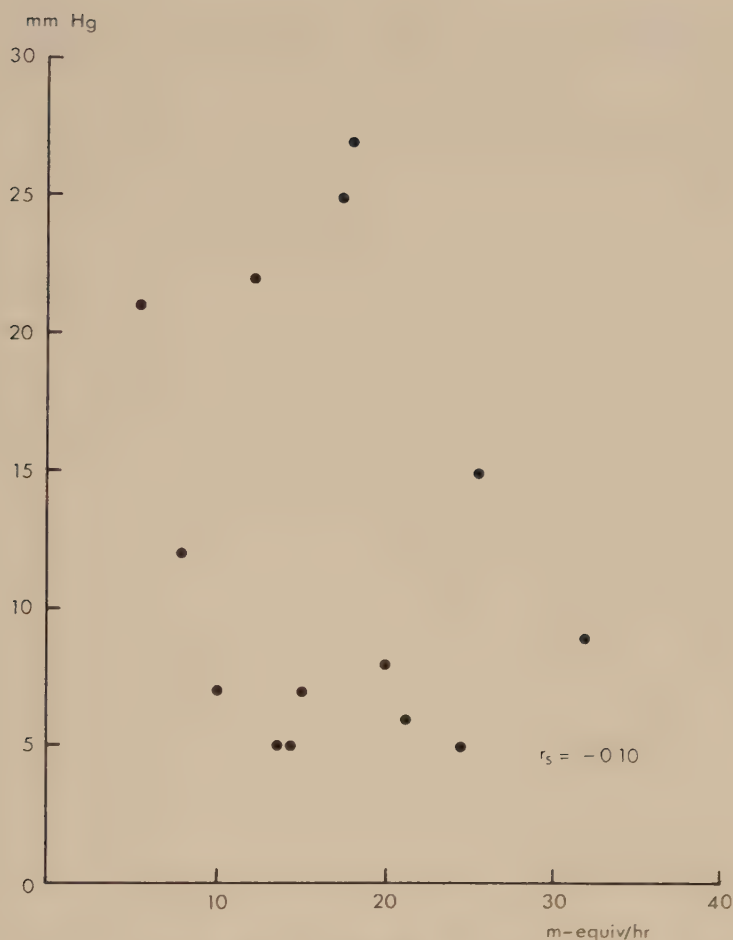


Fig. VII-7. The relationship between peak acid secretion (m-equiv/hr) and sphincter pressure (mm Hg) in patients with gastric ulcer.

have shown that the gastric mucosa contains neurogenic receptor mechanisms, the adequate stimuli of which are changes in acidity. Takeshima (1971) studied the discharge patterns in various vagal afferent fibres from the gastric wall to assess the transformation of applied stimulation into afferent discharge. The investigations were made in dogs and by means of the single fibre technique. Among the studied types of fibre there was one that carried tonic discharge, and the frequencies increased in accordance with the increase in the acidity of insufflated hydrochloric acid. Using the same technique Harding and Leek (1972) studied the activity from the cervical vagi of the anesthetized sheep. They found fibres that reacted with high-frequency spike discharge by application to the gastric mucosa of acid and al-

kali. The threshold value for hydrochloric acid was 15 to 50 m-equiv per l, and the latency 2 to 5 sec. The afferent activity in the vagus nerves is the probable cause of the reflectory changes in sphincter pressure which can be triggered off by application of acid to the mucosa of the proximal part of the stomach. The direct action was studied in anesthetized cats by Titchen and Wheeler (1971). They used both intact and decerebrated animals as well as spinal pithed preparations. Infusion of acid started contractions of the sphincter area after latencies of 30 to 90 sec. These were not obtained after the vagus nerves had been cut, and the study therefore allows the conclusion that the effect is exerted via a vago-vagal reflex. These results are consistent with the human studies carried out by Giles, Humphries, Mason, and Clark (1969). Perfusing the gastric aspect of the sphincter mucosa with hydrochloric acid was followed by an increase in sphincter pressure. The same studies were performed before and after giving atropine, and after atropine the effect of acid perfusion was abolished.

It is evident from the results of these studies that induced changes in the milieu of the stomach will affect the sphincter. An increase in acidity will reduce sphincter pressure – presumable through a reduction in serum gastrin. A local increase in acidity in the upper part of the stomach will exert the reverse effect via a vago-vagal reflex. It is not possible, however, on the basis of these clinical and experimental studies to draw parallel conclusions with regard to the condition in duodenal ulcer, chiefly because the amount of hydrochloric acid in the stomach was increased artificially. No such condition would ever occur in the human pathophysiology. In duodenal ulcer increased acidity is not the pathophysiological basis, but the result of a pathophysiological function of the factors responsible for the activity in the parietal cell mass. Of these factors the direct neurogenic activity in the vagus nerves and serum gastrin are the most essentials.

This complex of problems stands out in the work published by Castell (1971). He recorded changes in sphincter pressure during stimulation of acid secretion by intravenous injection of 0.2 U per kg of insulin. In a group of normal subjects he found no changes in pressure for the first 25 min, but a rapid decrease in pressure at the time of occurrence of hypoglycemic symptoms and resulting increased gastric acidity. It was concluded that the decrease in sphincter pressure suggests an absence of gastrin release in spite of the vagal stimulation indicated by the concomitant increase in gastric acid secretion. Later studies have shown, however, that this argumentation cannot be correct. The acid secretion provoked through hypoglycemia is the result of a direct vagal stimulation of the parietal cells and a direct vagal gastrin release combined with an indirect gastrin release (Stadil, 1972). Due to the direct regulation of the gastrin release via the antral acidity, serum gastrin will be dependent on the mode in which the insulin test is performed.

This is obvious from the studies carried out by Hansky, Korman, Cowley, and Baron (1972). In normal subjects, insulin hypoglycemia alone caused a significant rise in serum gastrin. During gastric aspiration, serum gastrin remained elevated for longer periods. Insulin hypoglycemia combined with bicarbonate neutralization induced a significant greater increase in serum gastrin. Durkin and Kucera (1972) and Feurle, Ketterer, Becker, Fuchs, and Creutzfeldt (1972) carried out similar studies in healthy subjects and also found a rise in serum gastrin in those individuals in whom the insulin test was performed without gastric aspiration. Hence it is clear that the fall in sphincter pressure cannot be caused by a drop in serum gastrin. Even though the original interpretation is thus no longer tenable Castell's (1971) studies are interesting seen in another perspective. Insulin-induced hypoglycemia leads to a decrease in sphincter pressure, an increase in gastric acid secretion, and an increase in serum gastrin. As the decrease in sphincter pressure is not consistent with the changes in serum gastrin there must be other factors involved. The most likely explanation would be that hypoglycemia stimulates the vagal fibres mediating inhibitory action on the sphincter, and that the effect of this factor must be greater than the stimulation resulting from the rise in serum gastrin.

With that possibility in mind it is of interest that Titchen and Wheeler (1971) demonstrated that electrical stimulation of the vagal nerves produced contraction as well as relaxation in the sphincter area. These studies were made on pithed, anesthetized or decerebrated cats which had both vagus nerves cut in the neck. The majority of investigators have focussed on the effect of electrical stimulation of the vagus nerves on the condition of the fundus but, the conclusions are the same. Electrical stimulation elicits both contraction and relaxation (Paton and Vane, 1963; Campbell, 1966; Bülbbring and Gershon, 1967; Beani, Bianchi, and Crema, 1971). Martinson (1965) in a series of reports elucidated the mechanism behind the varying response to electrical stimulation of the vagus nerves. He used anesthetized cats with a balloon in the corpus-fundus region, and recordings were made on the basis of volume changes at a constant intragastric pressure. These studies have shown that the vagus nerves contain two types of efferent fibre that are distinguishable in that they have different electrophysiological characteristics. The low-threshold group enhances gastric pressure, while the high-threshold group enhances secretion of acid and pepsin, increases blood flow in the stomach, and produces marked relaxation of the corpus-fundus region. This gastric relaxation was found not to be adrenergic but elicited by some unknown mechanism. As regards the relationship between the changes in fundic and sphincter pressure two studies are of particular interest. Arimori, Code, Schlegel, and Sturm (1970) made simultaneous recordings of the myogenic electrical activity of the sphincter, the myogenic electrical ac-

tivity of the fundus, and the intraluminal pressures. The studies were made in non-anesthetized dogs, and in the basal state there was a continuous activity in both regions. Distension of a balloon in the corpus of the esophagus reduced the phasic activity in both locations, and the intraluminal sphincter pressure decreased. Abrahamsson and Jansson (1969) have demonstrated that distension of the esophagus of chloralosed cats produced pronounced relaxation of the corpus-fundus region. This response was elicited as a vago-vagal reflex, using the high-threshold fibres as the efferent pathway. These studies demonstrate that the vagus nerves contain a set of fibres which at the same time release acid secretion and produce relaxation of the fundus and the gastroesophageal sphincter.

On the basis of the present knowledge of the regulation of the gastro-esophageal sphincter pressure it must be concluded that in duodenal ulcer neither changes in serum gastrin, nor enhanced activity in known reflex pathways can be held responsible for the changes in sphincter pressure. The most likely explanation is that the low sphincter pressure is the result of direct stimulation mediated through the vagus nerves and that, in consequence, it should be regarded as part of the pathophysiological complex in duodenal ulcer.

CHAPTER VIII

Effect of gastric surgery on gastroesophageal sphincter pressure

Introduction

Truncal or selective vagotomy, antrectomy, and resection of antrum and part of the parietal cell mass are the types of operation employed, either alone or in combination, in the surgical treatment of ulcers. Afferent impulses carried by the vagus nerves, serum gastrin and acidity of the gastric contents are factors known to be essential to the gastroesophageal sphincter pressure. I have therefore taken an interest in investigating whether gastric surgery affects the sphincter pressure and, whether the effect, if any, is consistent with the current concept of the neurogenic and hormonal regulation of the gastroesophageal sphincter.

Material

From December, 1970, to March, 1973, manometric studies were made in 124 patients, who had undergone gastric surgery. Recordings were technically unsatisfactory in two leaving a total material of 122 cases. These included partly patients in good health, partly patients with sequels, who had been admitted or reviewed in the outpatient clinic. The 78 patients in good health were reviewed from two to five months after operation. The 44 patients with sequels were reviewed from two months to 25 years after operation. Thirty-two patients in the last group were examined more than one year after surgery. The diagnostic programme is listed in table I.

The study covered three types of operation: Vagotomy and pyloroplasty, vagotomy and resection, and resection without vagotomy.

The vagotomy was performed as a truncal abdominal vagotomy in all cases. The material comprising patients who had undergone resection with or without vagotomy must be regarded as heterogenous since the extent of resections varied from antrectomy to resection of the distal three-quarters of the stomach. Both gastro-duodenal and gastro-jejunal anastomoses had been made.

The total material was grouped primarily according to type of operation. Secondly patients with vagotomy were divided into two subgroups accord-

Diagnostic examinations	No. of patients
X-ray, esophagus, stomach, and duodenum	44
X-ray, biliary tract	29
X-ray, colon	24
Esophagoscopy	18
Gastroscopy	39

Table VIII-I. The diagnostic programme in patients with sequels.

ing to the result of investigations of acid secretion. The patients without vagotomy were divided into three subgroups according to symptomatology and outcome of diagnostic examinations.

Hence the following groups appeared:

Incomplete vagotomy and pyloroplasty. Fourteen patients – one woman and 13 men. Ages varied from 30 to 67 years, with a mean age of 49 years. Indications for surgery showed the following distributions: duodenal ulcer – 11; prepyloric ulcer – two; dyspepsia without organic findings – one. Four patients had sequels; in one of them ulceration recurred, in the remaining three the symptoms were without any known organic cause. All of them had periodic attacks of epigastric pain, two had also heartburn, and one dysphagia.

Complete vagotomy and pyloroplasty. Twenty-four patients – four women and 20 men. Ages ranged from 20 to 78 years, with a mean age of 43 years. Indications for surgery showed the following distribution: duodenal ulcer – 19; duodenal and prepyloric ulcer – one; prepyloric ulcer – three; dyspepsia without organic findings – one. Four patients had sequels without any known organic cause. All of them suffered from periodic epigastric pain, and one also had experienced dysphagia.

Complete vagotomy and pyloroplasty. Group A. This group comprises 16 patients without acid secretion under basal condition.

Complete vagotomy and pyloroplasty. Group B. This group comprises the remaining eight patients with acid secretion under basal conditions.

Incomplete vagotomy and resection. Eight patients – all men – who varied in age from 30 to 65 years with a mean age of 48 years. Indications for surgery showed the following distribution: duodenal ulcer – six; dyspepsia without organic findings – two. One patient had undergone a simultaneous cholecystectomy because of gallstones. Six patients had sequels without any known organic cause. All of them had periodic epigastric pain and in addition one of them had dysphagia.

Complete vagotomy and resection. Twenty-four patients – six women and 18 men. Ages ranged from 29 to 71 years, with a mean age of 43 years. Indications for surgery were distributed as follows: duodenal ulcer – 17; prepyloric ulcer – four; gastric ulcer – one; dyspepsia without any organic findings – two. One patient had undergone a simultaneous cholecystectomy because of gallstones. Six patients had sequels without any known organic cause. They all suffered from periodic epigastric pain; furthermore, three had heartburn, and one dysphagia.

Gastric resection. Group A. Twenty-eight individuals, who had neither been readmitted, nor reviewed in the outpatient clinic because of sequels. There were nine women and 19 men. The youngest was 32 and the oldest 72 years, with a mean age of 54 years. Indications for surgery had been: duodenal ulcer – 13; duodenal and gastric ulcer – three; prepyloric ulcer – one; cancer of the stomach – two; dyspepsia without organic cause – one. Simultaneous cholecystectomy had been performed in four cases.

Gastric resection. Group B. The five patients in this group had been readmitted because of sequels attributable to known organic causes. Three had recurrent ulceration, one an afferent reflux syndrome, and one had esophageal peptic stricture.

Gastric resection. Group C. The 19 patients in this group had been reviewed in the outpatient clinic or readmitted with sequels without any known organic cause. There were five women and 14 men. Ages varied from 29 to 74 years, with a mean age of 53 years. Indications for surgery showed the following distribution: duodenal ulcer – 12; prepyloric ulcer – one; gastric ulcer – three; dyspepsia without organic findings – three. Four of them had undergone a simultaneous cholecystectomy because of gallstones. All of them suffered from periodic attacks of epigastric pain, and in addition two had heartburn and three dysphagia.

Before and after resection. This group comprises 22 patients, five women and 17 men. They varied in age from 32 to 72 years, with a mean age of

52 years. Indications for surgery showed the following distribution: duodenal ulcer – eight; duodenal and gastric ulcer – two; prepyloric ulcer – two; gastric ulcer – ten. Postoperatively, two patients had sequels without any known organic cause. These two patients are included in the calculations in gastric resection, group C.

Methods

The *manometric studies* were carried out as detailed in chapter IV.

Determination of *the basal and the pentagastrin-stimulated acid secretion* was made as described in chapter VII.

The following modification of *the insulin test* was used: The fasting patient was intubated and the radio-opaque nasogastric tube positioned fluoroscopically into the stomach. The fasting gastric secretion was aspirated. Basal secretion was collected for four 15-min periods, and this was followed by eight 15-min collections after intravenous injection of 0.2 I.U. of insulin per kg body weight. The secretion from the 15-min periods was measured for volume, pH, and acid concentration. The acid concentration was determined by titration with 0.1 n NaOH to pH 3.5. A rise in acid concentration in the first hour after insulin of more than 20 m-equiv per l of the basal secretion, and of more than 10 m-equiv per l if no basal secretion was present was taken as a positive response.

In the patients who underwent vagotomy acid secretion was studied three months after operation. After vagotomy and pyloroplasty the vagotomy was accepted as complete if the insulin test was negative, and if, after administration of pentagastrin, peak acid secretion was not higher postoperatively than preoperatively. After vagotomy and resection the vagotomy was accepted as complete if the operation induced a fall in the pentagastrin-stimulated peak acid secretion of at least 85 per cent.

Results

Fig. 1 lists the sphincter pressure recorded in each patient in the groups with vagotomy and pyloroplasty, and table II shows the various characteristics of sphincter pressure in these groups. Mean sphincter pressure in the group with incomplete vagotomy does neither differ from that in the total material of complete vagotomy nor from that in the normal material. Mean pressure in the group with complete vagotomy is not different from mean in the normals. In group A the mean pressure is higher than in the normal material ($0.05 > p_{MW}$) and also higher than in group B ($0.01 > p_{MW}$). In the latter group the mean sphincter pressure is lower than in the normal material ($0.01 > p_{MW}$).

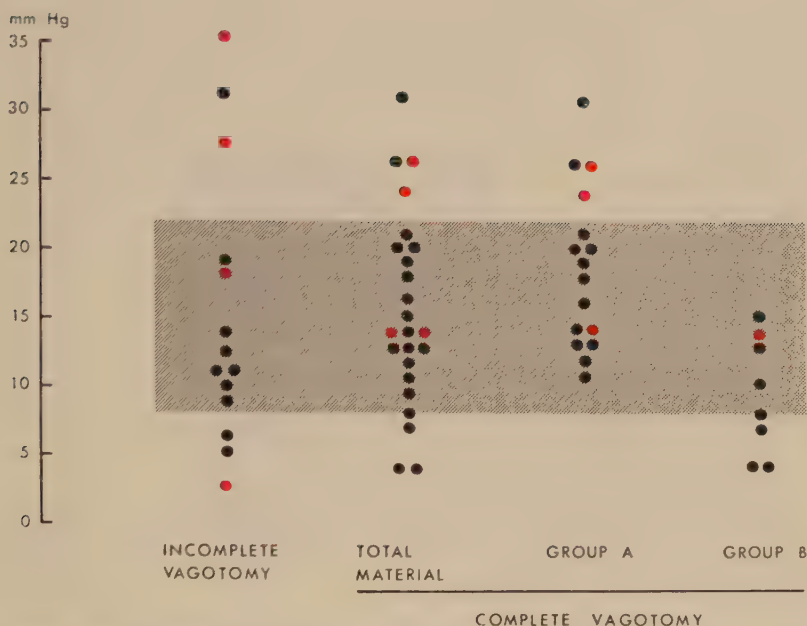


Fig. VIII-1. Each individual sphincter pressure after vagotomy and pyloroplasty. Red circles indicate patients with sequels. Subgrouping according to criteria mentioned in the text.

	n	Mean	Range
Complete vagotomy (total material)	24	16	4-31
Incomplete vagotomy	14	15	2-35
Complete vagotomy (group a)	16	19	11-31
Complete vagotomy (group b)	8	9	4-15

Table VIII-II. Characteristics of sphincter pressure (mm Hg) after vagotomy and polyroplasty. Subgrouping according to criteria mentioned in the text.

Fig. 2 lists the sphincter pressure recorded in each patient in the groups with vagotomy and resection, and table III shows the various characteristics of sphincter pressure in these groups. After incomplete vagotomy the

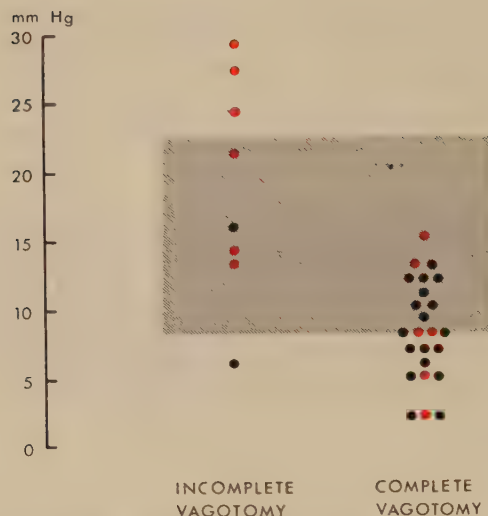


Fig. VIII-2. Each individual sphincter pressure after vagotomy and resection. Red circles indicate patients with sequels.

	n	Mean	Range
Incomplete vagotomy	8	19	6-29
Complete vagotomy	24	8	2-15

Table VIII-III. Characteristics of sphincter pressure (mm Hg) after vagotomy and resection.

mean sphincter pressure is higher than after complete vagotomy ($0.01 > p_{MW}$) but does not differ from that of the normal material. After complete vagotomy the mean sphincter pressure is lower than in the total material of complete vagotomy and pyloroplasty ($0.01 > p_{MW}$), and lower than in the normal material ($0.01 > p_{MW}$).

Fig. 3 lists the sphincter pressure recorded in each patient in the groups with resection without vagotomy, and table IV shows the various characteristics of sphincter pressure in these groups. In group A the mean sphincter pressure is lower than in the normal material ($0.01 > p_{MW}$). In group C the mean sphincter pressure is higher than in the normal material ($0.01 > p_{MW}$), and higher than in group A ($0.01 > p_{MW}$). In group C acid secretion was studied in 14 out of 19 patients. There was no acid secretion under basal conditions in 11, ten of whom had achlorhydria.

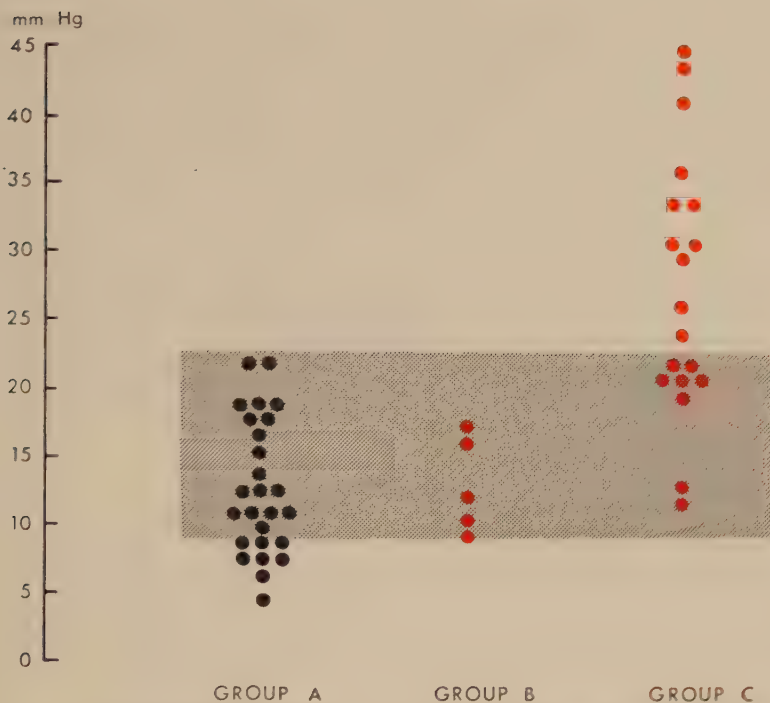


Fig. VIII-3. Each individual sphincter pressure after resection without vagotomy. Red circles indicate patients with sequels. Subgrouping according to criteria mentioned in the text.

	n	Mean	Range
Group A	28	12	4-21
Group B	5	--	--
Group C	19	27	11-44

Table VIII-IV. Characteristics of sphincter pressures (mm Hg) after resection without vagotomy. Subgrouping according to criteria mentioned in the text.

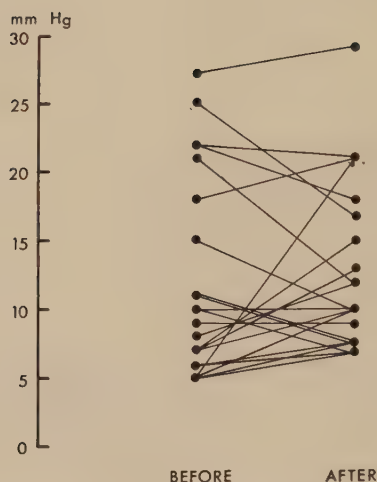


Fig. VIII-4. Each individual sphincter pressure in 22 patients before and after resection without vagotomy.

	n	Mean	Range
Preoperative	22	12	5-27
Postoperative	22	13	7-29

Table VIII-V. Characteristics of sphincter pressure (mm Hg) in 22 patients before and after resection without vagotomy.

Fig. 4 lists the sphincter pressure recorded in 22 patients before and after resection without vagotomy. Table V shows the various characteristics of sphincter pressure. There is no difference between the pre- and postoperative mean sphincter pressure. Two patients, the one with the highest postoperative sphincter pressure and one of those with the second-highest value, have later been examined for sequels without any known organic cause.

It should be added that in the majority of the patients classified as suffering from »sequels without any known organic cause« (occurred after all three types of operation) gastroscopy revealed diffuse changes in the gastric mucosa, ranging from mild hyperemia and edema over hypertrophy with pseudopolypoid and granulomatous formation to atrophy.

Following vagotomy with either pyloroplasty or resection a total of 19 patients had sequels without any known organic cause, and dysphagia was part of the symptomatology in four. These patients were viewed two, three, four, and eight months, respectively, after operation. All of them had a normally relaxing sphincter and a normally propagating peristaltic wave on swallowing. One of the patients without sequels had insufficient relaxation on swallowing.

Of the 19 patients with sequels without any known organic cause following resection without vagotomy three had dysphagia. Swallowing elicited simultaneous contractions in the corpus of the esophagus in all three, and sphincter relaxation was insufficient in one. In the group of patients not suffering from sequels there was one case of insufficient relaxation.

Discussion

The present study demonstrates that after complete, truncal vagotomy and pyloroplasty mean sphincter pressure is not different from that in the normal material. After complete, truncal vagotomy and resection mean sphincter pressure is lower than after complete vagotomy and pyloroplasty, and also lower than in the normal material. The basis materials are heterogenous since they comprise patients with ulcers of different localization as well as patients without. The size of the subgroups did not allow processing, and it is not possible to draw conclusions with regard to the direct effect of these two types of operation on sphincter pressure.

Many investigators have studied the sphincter pressure in patients who have undergone truncal vagotomy, and compared the values with those recorded in normal subjects or subjects with intact ulcerated stomachs. Crispin *et al.* (1967), using perfused catheters, investigated sphincter pressure in ten patients with peptic ulcer before and after vagotomy combined with a drainage procedure. Mean sphincter pressure was unchanged after operation and not different from that in normal subjects. Insulin tests were not performed. Mann and Hardeastle (1968), using non-perfused catheters, found that mean sphincter pressure in four patients admitted with sequels to vagotomy and pyloroplasty did not differ from that in a group of nine patients with duodenal ulcer. Christiansen, Borgeskov, Lockwood, and Aagaard (1970) used the same technique in a study of 13 patients with duodenal ulcer before and after vagotomy combined with a drainage procedure. The insulin test, according to the criteria of Hollander, was negative in 12 patients, and sphincter pressures were found to be normal both before and after operation. Blackman, Rakatansky, Nasrullah, and Thayer (1971), using perfused catheters, found that vagotomy with a drainage procedure was without effect on mean sphincter pressure; preoperatively the range was

stated to be 4 to 28 mm Hg, whilst postoperatively it was 4 to 26 mm Hg. The completeness of vagotomy was substantiated in each case by an insulin test. Earlam and Thomas (1972), using balloon-technique and non-perfused catheters, in a study of 28 patients with duodenal ulcers observed that vagotomy and pyloroplasty or gastroenteroanastomosis did not affect mean sphincter pressure, whilst in a group of nine patients with duodenal ulcer, distal gastrectomy with or without vagotomy was followed by a significant reduction in mean pressure.

Considerable caution should be exercised in drawing comparisons between the results of these investigations. The basis materials are not homogenous, and different methods have been used in recordings of pressure. It is a common findings, however, that complete vagotomy with a drainage procedure does not influence mean sphincter pressure in any great measure. The pressures after complete vagotomy and resection have not been studied in detail previously but, the present study clearly demonstrates that this operative intervention is followed by a reduction in sphincter pressure.

These results are well in keeping with the current concept of hormonal control of the gastroesophageal sphincter. Lipshutz *et al.* (1972) demonstrated that serum gastrin is essential to the maintenance of normal resting sphincter pressure in opossum. They found that increasing amounts of gastrin antiserum produced a graded inhibition in sphincter pressure, the maximum inhibition representing a 80 per cent reduction.

Several investigators have studied serum gastrin after truncal vagotomy and pyloroplasty or resection. Trudeau and McGugian (1971a), in 65 patients with duodenal ulcer, investigated serum gastrin before and after vagotomy and pyloroplasty, and found that mean serum gastrin was unchanged after operation, whilst in 41 patients treated with vagotomy and resection there was a 77 per cent reduction. Korman, Hansky, and Scott (1972) found that mean serum gastrin was higher in 50 patients after vagotomy and pyloroplasty than in 70 non-operated patients with duodenal ulcer. The completeness of vagotomy was tested in 21 cases and found to be complete in 20 of them. Stern and Walsh (1972), in nine patients, found that mean serum gastrin was higher after vagotomy and pyloroplasty than in patients with duodenal ulcer, and higher than in normal subjects. In a group of eight patients, who had undergone vagotomy, distal resection and gastrojejunostomy, mean serum gastrin was lower than in patients who had undergone vagotomy and pyloroplasty, and lower than in normal subjects. Stadil (1972) compared mean serum gastrin in 23 non-operated patients with prepyloric or duodenal ulcer with that in 44 patients treated with vagotomy and pyloroplasty. After complete vagotomy the mean was not significantly different from that in non-operated cases. After incomplete vagotomy the mean was higher than in the unoperated cases.

Even though there are minor divergences between these findings, the trend is clear. After complete vagotomy and pyloroplasty the serum gastrin level is of the same magnitude, or a little higher, as in patients with juxtapyloric ulcers and normal subjects. After vagotomy and resection the level is lower than in patients with intact, ulcerated stomachs, and lower than in normal subjects. The operatively induced changes in serum gastrin are followed by corresponding changes in sphincter pressure, and the results of the present manometric studies are thus in line with those of Lipshutz *et al.* (1972) as regard the importance of endogenous gastrin on sphincter pressure. Furthermore, these results supplement the studies which demonstrated that procedures causing a liberation of endogenous gastrin are followed by an increase in sphincter pressure (Castell and Harris, 1970; Castell and Levine, 1971; Lipshutz *et al.* 1972).

In the present study patients with acid secretion under basal conditions after vagotomy and pyloroplasty were found to have a lower mean sphincter pressure than those without. McGuigan and Trudeau (1972), in 24 patients, compared serum gastrin and basal acid secretion after vagotomy and pyloroplasty. The completeness of vagotomy was not tested. There was no difference in mean serum gastrin between the groups – basal acid secretion higher than 2 m-equiv per hr and – basal acid secretion lower than 2 m-equiv per hr. No mention was made of serum gastrin in patients without acid secretion under basal conditions, and it remains obscure whether the observed difference in mean sphincter pressure is attributable to changes in serum gastrin.

It was to be expected that distal resection of the stomach without vagotomy would be followed by a reduction in sphincter pressure but, this came through in part only. Patients in good health had a lower mean pressure than normal subjects whilst those with sequels without any known organic cause had a higher mean sphincter pressure than those without sequels, and higher than in normal subjects. The reason for the higher values in the latter group is not clear and they do not occur in previously published materials on this type of operation. Mann and Hardcastle (1967), using non-perfused catheters, investigated sphincter pressure in 14 patients after distal gastrectomy without vagotomy. They found the mean pressure to be lower than in the normal material. As mentioned in the foregoing Earlam and Thomas (1972), using balloon-technique and nonperfused catheters, found the mean pressure to be significantly reduced after distal gastrectomy with or without vagotomy. This difference in findings may in part be ascribed to the fact that these authors used a technique essentially different from that applied in the present study.

The cause of the high pressure is not likely to be found in a high serum gastrin level. In all cases of resection at least antrectomy was performed,

and the antrum is held responsible for about half of the endogenous production of gastrin. Stadil and Rehfeld (1972) found that mean serum gastrin in 15 patients treated with distal gastrectomy was about half the normal mean.

One explanation may be that a high sphincter pressure is a disease entity *per se* and consequently the major cause of the symptoms. This view is supported by the findings of Ellis *et al.* (1964). They employed myotomy in 12 cases of hypertensive sphincter with or without spastic esophagus. The stomach was intact in all cases, and pain and dysphagia were prominent features of the preoperative symptomatology. The response was stated to be satisfactory in ten of the cases, and this would suggest that in some instances a high sphincter pressure may be responsible for the symptoms.

Another explanation may be that a high pressure is secondary to pathophysiological conditions in the stomach or the remaining part of the abdomen and elicited via afferent impulses passed via the vagal nerves. This concept is supported by the gastroscopic findings in combination with the distribution of sphincter pressures in the various groups of the present study. Gastroscopy of those patients with sequels of obscure origin (following all three types of operation) revealed mucosal changes of varying severity. In many cases the changes were so severe that they could immediately be accepted as cause of pain. On the other hand, the inavailability of a reference material – the patients in good health did not undergo gastroscopy – renders it difficult to draw conclusions at the present stage. In the group of patients with sequels to complete vagotomy and pyloroplasty or resection sphincter pressures were distributed as in patients in good health. Patients with sequels to vagotomy and resection and a partially preserved innervation of the residual stomach tended to have a higher sphincter pressure. Patients with sequels predominated in the group of incomplete vagotomy and resection, and mean sphincter pressure was higher in this group than in the group of complete vagotomy and resection. In the group of patients with sequels to resection without vagotomy the mean sphincter pressure was clearly higher than in patients in good health and normal subjects.

On the evidence of these findings it seems reasonable to assume that changes in the stomach remnant, reflectorily via the vagus nerves – elicit tension changes in the gastroesophageal sphincter. This theory is supported by previously published reports dealing with: afferent impulse conduction over the vagus nerves in response to stimuli applied to the stomach, – tension changes in the sphincter elicited by chemo- and mechano-stimuli to the stomach, and – changes in sphincter pressure in response to spontaneously occurring tension changes in the corpus-fundus region.

Systematic studies of afferent impulses carried by the vagus nerves have been published by Paintal (1954), Iggo (1955), Anand and Pillai (1967), Nijima (1967), Takeshima (1971), Davison (1972), and Harding and

Leek (1972). These authors have demonstrated that stimulation of receptors in the stomach is followed by impulses in the vagus nerves. The vagus nerves are afferent pathways for chemo- and mechanoreceptors in the gastric mucosa, and for mechanoreceptors in the muscle layers.

The effect of central stimulation of the vagus nerves on the sphincter pressure and the corpus of the esophagus has been studied by Carlson *et al.* (1922), Dey, Gilbert, Trump, and Roskelley (1946), and Titchen and Wheeler (1971). It has been proved that artificially induced afferent activity in the vagus nerves is followed by changes in the length of corpus esophagei and in the sphincter pressure. Moreover, it has been substantiated that the vago-vagally induced increase in sphincter pressure is elicited via stimuli to cholinergic receptors. The afferent fibres in the vagus nerves have different anatomical and electrophysiological characteristics, and the simultaneous activation of different types of fibre is likely to be the cause of the fact that contraction as well as relaxation can be elicited (Titchen and Wheeler, 1971).

Carlson *et al.* (1922), Dey *et al.* (1946), Clark and Vane (1961), and Titchen and Wheeler (1971) studied the direct effect of mechanical stimulation of the stomach on sphincter pressure. They showed that moderate mechanical stimulation and distension of the stomach entail an increase in sphincter pressure, and that this reflex is elicited via the vagus nerves. By augmenting the intensity of stimulation the reaction shifts from contraction to relaxation. The relaxation must be regarded as a non-physiological reaction, and as part of the vomiting reflex.

This relation between the corpus-fundus region and the gastroesophageal sphincter is also evident from studies of the relationship of spontaneously occurring tension changes in the corpus-fundus region to sphincter pressure (Cannon and Washburn, 1911; Carlson and Luckhardt, 1914; Carlson *et al.* 1922; Lind *et al.* 1961; Diamant and Akin, 1972). Diamant and Akin (1972) studied simultaneous pressure variations in the gastroesophageal sphincter and upper and lower stomach in unanesthetized dogs. They observed a marked increase in sphincter pressure in connection with pressure increase in the upper part of the stomach, and the change in sphincter pressure was closely related to the changes in intragastric pressure, in a ratio of approximately 8:1. The authors mention preliminary studies which shows that truncal vagotomy abolishes the sphincter response to increase in intragastric pressure, and suggest that the effect is elicited by afferent impulses in the vagus nerves.

On the evidence of these findings it may be concluded that spontaneous and induced changes in the stomach affect the sphincter pressure via the vagus nerves. Chemo- and mechanoreceptors are present in the gastric mucosa and, according to the theory advanced in the foregoing, the observed mucosal

changes seem to be the point of origin of the abnormal reflex activity. Still according to this theory: The mucosal changes are either stimuli *per se*, or they affect the receptors making them more sensitive to gastric contents. However, reflexes elicited by acid stimulation cannot be of importance in the present material. Of the 19 patients with sequels to resection without vagotomy acid secretion was investigated in 14, 11 of whom proved to have no basal acid secretion. Gastro-duodenal anastomoses render reflux from the small intestine possible, and after gastro-jejunal anastomoses the stomach remnant is involved in the normal passage. Therefore it is possible that the reaction of the small intestine contents or enzymes act as stimuli. However, it has to be mentioned that the above described theory is weakened by the fact that patients in good health did not undergo gastroscopy.

The present material also demonstrate, that distal resection of the stomach without vagotomy was not followed by a fall in mean sphincter pressure. Stadil and Rehfeldt (1972) found that mean serum gastrin in patients treated with distal gastrectomy was about half the normal mean and, according to the accepted importance of serum gastrin for sphincter pressure, it was to be expected that this operation would entail a fall in mean pressure. Concerning the explanation of the result there are two possibilities. Firstly, – serum gastrin is not that important for maintenance of resting sphincter pressure as previously thought, and secondly, – a decrease in sphincter pressure conditioned by a fall in serum gastrin is compensated by another mechanism, for instance an increase in pressure mediated via vago-vagally reflexes.

Dysphagia is a common sequel to vagotomy. It may occur after thoracic vagotomy (Grimson, Baylin, Taylor, Hesser, and Rundles, 1947) after truncal abdominal vagotomy (Tanner, 1951; Bruce and Small, 1959; Guillory and Clagett, 1967; Williams and Woodward, 1967; Edwards, 1970; Ruckley, Falconer, Small, and Smith, 1970) and after selective gastric vagotomy (Ruckley *et al.* 1970). The incidence varies considerably. Many reports do not mention this complication at all, others state frequencies of between ten and 37 per cent (Grimson *et al.* 1947; Bruce and Small, 1959; Williams and Woodward, 1967; Ruckley *et al.* 1970). Postlethwait, Kim, and Dillon (1969) collected more than 5000 cases of abdominal vagotomies from the literature and calculated the incidence of various complications. They found that dysphagia was reported in 3.6 per cent of the cases.

It is generally accepted that there are two different organic causes of dysphagia. One is an extra- or intramural fibrosis developing from edema and hematoma following dissection around the lower part of the esophagus. The other is a peptic stricture. Cases in which these organic causes cannot be verified are believed to have a functional pathogenesis. The last mentioned type is by far the most frequent, and the clinical course is characteristic. It

starts one or two weeks after operation, occasionally in connection with removal of the probe and change to solid food but most often the patients has ingested solid food for several days without experiencing discomfort. The intensity increases over a short period only to decrease and vanish spontaneously. The dysphagia may be so pronounced for a short while that parenteral nutrition is required. Radiological examination of the corpus of the esophagus reveals slight dilatation with smooth transition to a terminal narrowing. Esophagoscopy shows a normal mucosa; occasionally a slight increased resistance is noted when passing the esophagoscope into the stomach.

The cause of this transitory dysphagia is not known but two theories have been advanced. One is that intra- or extramural edema and hematoma entail a temporary resistance against the passage of food. As resorption takes place the esophagus regains its usual elasticity and the dysphagia abates. The other possibility is that in some cases the vagotomy involves denervation of the sphincter area and the lower part of the esophagus, resulting in simultaneous contractions and failing relaxation of the sphincter on swallowing.

There are only a few reports dealing with the manometric characteristics of these patients. Anderson, Schlegel, and Olsen (1966), using balloon-technique and non-perfused catheters, studied 15 patients with dysphagia following vagotomy. In five of them relaxation was insufficient on swallowing. Edwards (1970) studied three patients by means of balloon-technique. In all of them dry swallowing produced a normally propagating peristaltic wave in the corpus and normal relaxation of the sphincter. Fluid intake elicited repetitive and simultaneous contractions in the corpus in one of them. The author concluded that these contractions were elicited by a distal mechanical hinderance of passage. Guillory and Clagett (1967) made a manometric study of one patient and found the same characteristics. On subesquent operation a considerable scarring was found at the hiatus. The scar was excised and postoperatively the patient was able to swallow without difficulty.

The results of the manometric studies of the present material do not contribute to a clarification of the cause. There were four cases of dysphagia following vagotomy in combination with either pyloroplasty or resection, and in all of them dry swallowing was accompanied by a normally propagating peristaltic wave and normal relaxation of the sphincter. As regards the three patients who developed dysphagia after resection without vagotomy the pathophysiology is clear – all of them presented the manometric characteristics of a spastic esophagus.

So far the manometric studies have not given the final answer to the problem of dysphagia following vagotomy, but the results hitherto obtained are not in support of the theory of a general neurogenic cause. In this context

it should be borne in mind that relaxation is not synonymous with opening. Normal relaxation means that the muscular resistance against the passing of food is eliminated, but for the food to pass it is also necessary that the esophagus is so resilient that it permits distension in conjunction with the passing of the bolus.

The supporters of the neurogenic theory adduce that if the vagotomy is performed at a high level it will involve cutting of nerves to the sphincter area. Their argumentation is based on both clinical and preclinical studies. In the work published by Grimson *et al.* (1947) the vagotomies performed were transthoracic; the frequency of dysphagia was 37 per cent, which is appreciably higher than after transabdominal vagotomy. Animal experiments have shown unambiguously that high level vagotomy is followed by functional disturbance in the sphincter area. Different types of operation have been used. They include – bilateral cervical vagotomy, hilar vagotomy, and resection of the esophageal branches of the vagus nerves (Carveth, Schlegel, Code, and Ellis, 1962), – sympathetic extirpation combined with bilateral subhilar vagotomy (Greenwood, Schlegel, Code, and Ellis, 1962), – transabdominal vagotomy (Elebute, Kelley, and Schwartz, 1966), – subhilar vagotomy (Arimori *et al.* 1970), and – periesophageal vagotomy (Burgess, Schlegel, and Ellis, 1972). These animal experiments confirm that high level vagotomy is entailing temporary functional disturbances in the gastroesophageal sphincter. However, it is not possible to apply these results to human pathophysiology because in man the vagotomy – be it transthoracic or transabdominal – is performed at a lower level. Parasympathetic denervation of the gastroesophageal sphincter can therefore not be the cause of dysphagia in general, although it cannot be excluded that denervation may be the cause in a few individuals, in whom the course of the vagus nerves to the sphincter area is abnormal.

Leaving out of account the cases with a known organic cause it may be concluded that the cause or causes of the dysphagia following vagotomy remain obscure. On the evidence of the clinical course, manometric characteristics and animal experiments it may be assumed, however, that the most frequent cause is a temporary mechanical hindrance of passage resulting from lesion of the surrounding tissue during vagotomy.

CHAPTER IX

Gastroesophageal sphincter pressure in patients with diseases of the biliary tract

Introduction

Patients with diseases of the biliary tract very often present with a varied clinical picture. In addition to the classic colicky pain, they often display symptoms which are usually accepted as being elicited from the stomach or esophagus. It has therefore been of interest to investigate the gastroesophageal sphincter pressure in a material of patients with diseases of the biliary tract.

Material

In the period December, 1970, to Juli, 1973, manometric studies were made of 128 patients with surgically verified *gallstones*. Recordings were technically unsatisfactory in seven, and the processed material thus comprises 121 cases.

It was a condition for acceptance in the material that the patients had not previously undergone gastric surgery, and that neither the preoperative examinations, nor the operation on the biliary tract had revealed organic changes in the stomach.

The material comprises 106 women and 15 men. Ages varied from 18 to 77 years, with a mean age of 47 years.

Of total 121 patients 16 had heartburn, and 13 had noticed periodic dysphagia.

Radiological examination of the stomach had been done in 52 patients, and a hiatus hernia demonstrated in three.

In the period December, 1970, to September, 1973, manometric studies were made of 74 patients *before and after cholecystectomy*.

The material comprises 64 women and ten men. Ages varied from 19 to 77 years, with a mean age of 49 years. Operation had revealed stones in the gallbladder in all patients except one, and seven of them also had stones in the common duct.

Of total 74 patients, 14 suffered from heartburn before the operation, and 11 had occasionally experienced dysphagia.

In 64 of the patients the postoperative manometric studies were made one to nine months after the operation, and in the remaining ten 15 to 20 months after the operation.

In the period December, 1970, to September, 1973, manometric studies were also made of 48 patients admitted, or examined in the outpatient clinic, because of a *postcholecystectomy syndrome*. Recordings were technically unsatisfactory in two cases, and the processed material thus comprises 46 cases. All cases fulfilled the following criteria:

1. No previous gastric operations had been performed
2. Pain in the upper abdomen was part of the symptomatology
3. Intravenous cholangiography and radiological examination of the stomach had been performed
4. The above mentioned diagnostic examinations had not revealed ulcer of the stomach or duodenum, or stones in the common duct

There were 40 women and six men. Ages varied from 24 to 79 years, with a mean age of 56 years.

In addition to pain, six had also heartburn, and 11 periodic dysphagia.

Radiological examination of the stomach had revealed hiatus hernia in 11 cases.

Method

The *manometric studies* were carried out as described in chapter IV.

Results

Gallstones: Fig. 1 lists the sphincter pressure of each patient in relation to the normal area, and table I shows the characteristics of sphincter pressure. The difference between means in normal subjects and in the patient material is not significant. Sixteen patients had a pressure that is below the lower limit of normal whilst in 28 it is above the upper limit of normal.

All 16 patients with heartburn had a pressure that is lower than 15 mm Hg.

Of the 13 patients with dysphagia four had insufficient relaxation of the sphincter on swallowing. There were no cases of spastic esophagus. Out of the remaining 108 patients four had insufficient relaxation of the sphincter. There were no cases of spastic esophagus in this group either.

Before and after cholecystectomy: Fig. 2 shows each sphincter pressure before and after cholecystectomy, and table II lists the characteristics of the sphincter pressures. The preoperative mean pressure is equal to the post-

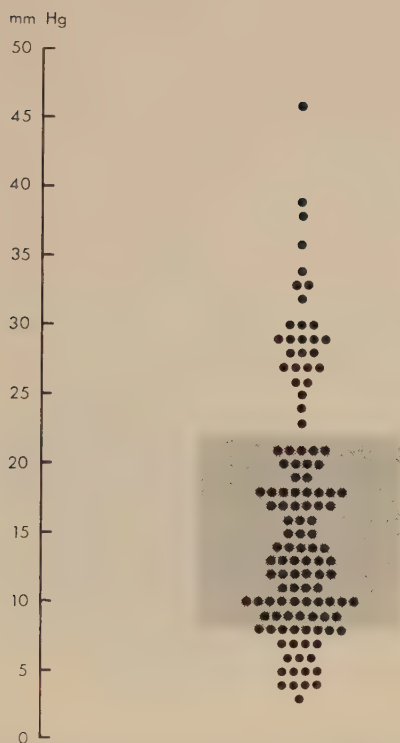


Fig. IX-1. Each sphincter pressure in patients with gallstones in relation to the normal area (hatched).

n	Mean	Range	$p\chi^2$
121	16	3-46	0.001)p

Table IX-1. Characteristics of sphincter pressure (mm Hg) in patients with gallstones.

operative mean. Before operation, 41 patients had a normal pressure. After operation the corresponding figure is 50. This difference is not significant.

The preoperative recordings showed 22 cases of pressures above the upper limit of normal. The postoperative recordings showed 17 cases, of which seven also had a hypertensive sphincter before the operation.

The 14 patients with heartburn before the operation all had a pressure of less than 15 mm Hg. Preoperatively seven patients had insufficient relaxation of the sphincter on swallowing. Postoperatively there were also seven, in four of whom relaxation was insufficient both pre- and postoperatively. There were no cases of spastic esophagus.

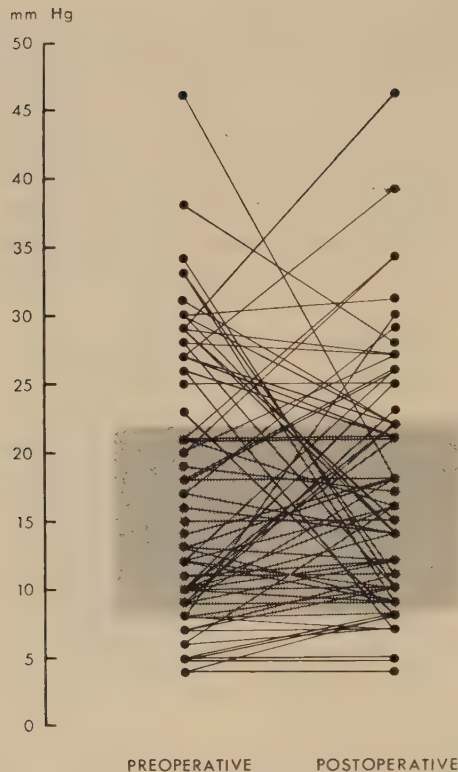


Fig. IX-2. Each sphincter pressure before and after cholecystectomy. The hatched area indicates the normal area.

	n	Mean	Range	$p\chi^2$
Preoperative	74	17	4-46	0.001)p
Postoperative	74	17	4-46	0.005)p

Table IX-II. Characteristics of sphincter pressures (mm Hg) before and after cholecystectomy.

Of the 17 patients with a hypertensive sphincter after operation, seven stated to be in good health and without symptoms from the upper abdomen. The remaining ten stated that they had had periodic attacks of pain in the upper abdomen. All these patients were checked two to four months after the operation.

Postcholecystectomy syndrome: Fig. 3 shows each sphincter pressure, and

subjects ($0.001 > P_{\text{atu}}$, $0.001 > P_{\text{MW}}$). The mean pressure in patients with hernia does not differ from that in normal subjects.

Among the six patients with heartburn one had a pressure of 27 mm Hg, whilst the remaining patients had pressures below 15 mm Hg. There were 12 cases with insufficient relaxation of the sphincter on swallowing and one showed the characteristics of a spastic esophagus. . . .

Discussion

The results of the present study demonstrate that mean sphincter pressure in patients with gallstones is of the same magnitude as in normal subjects. The distribution of sphincter pressures in patients, however, is different from that in normal subjects. This difference results from the fact that part of pressures in the patient group are either below the lower limit or above the upper limit of normal.

Sphincter pressure has not previously been studied in patients with gallstones. Tapiovaara and Siurala (1958) reported a frequent coincidence of diseases of the biliary tract and abnormal findings on radiological examination of the stomach. The abnormal findings include hypertonia, difficulties in emptying, spastic antrum, spastic bulbus duodeni and air in the bulbus. Jasienski (1966) studied intragastric pressure in normal subjects and patients with gallstones. In the patients with gallstones there were irregular variations in the basal intragastric pressure. Likewise the peristaltic contractions were irregular, occurring with varying frequency and occasionally with very high amplitudes. In view of the close functional relation between the stomach and the gastroesophageal sphincter patients with gallstones may be expected to have an abnormal gastroesophageal sphincter pressure.

It should be borne in mind that the occurrence of gallstones as well as the abnormal sphincter pressure may indicate admission to hospital. In consequence, it is not possible to apply the frequency of simultaneous occurrence in hospital materials to the total population of patients with gallstones.

It is also evident from the results of the present study that, in some patients, cholecystectomy is accompanied by great changes in sphincter pressure. However, in the total material the mean pressure after cholecystectomy is not different from that in normal subjects. Moreover, it appears that in patients with the postcholecystectomy syndrome without hiatus hernia the mean pressure is higher than in normal subjects.

Sphincter pressures have not previously been studied in similar materials, but the investigations carried out by Southam (1969) are of interest. He studied the effect of cholecystectomy in seven patients, all of whom had heartburn and a positive acid perfusion test. After operation the acid per-

fusion test was negative in all cases, five patients were free of symptoms, whilst two still had mild symptoms from the esophagus. A likely explanation of these results will be that, in some cases, cholecystectomy is followed by an increase in the capacity of the sphincter to resist reflux.

On the basis of previously reported studies there is some reason to believe that pathophysiological changes in the biliary tract may influence the stomach and the gastroesophageal sphincter – either reflectorily or via changes in the hormonal balance.

The anatomical basis for an afferent reflex activity from the liver and biliary tract is present. Inoue (1955), Tsai (1958), Kimura (1966) and Tanikawa (1968) described sensory nerve endings in the liver, common duct, cystic duct and gallbladder. The sensory filaments run in the splanchnic as well as in the vagus nerves. These sensory nerve filaments transmit impulses from receptors, the adequate stimuli of which have been studied by Nijima (1959), Okino (1959), Newmann and Paul (1966), Andrews and Palmer (1967), Andrews and Stratmann (1968), Nijima (1969) and Nijima (1969a). These authors have demonstrated that the liver parenchyma contains gluc- and osmoreceptors, and the biliary tract chemo-, mechano- and tensionsreceptors.

The anatomical and physiological basis for reflexes elicited from the liver and the biliary tract is thus present, but there are only a few studies on reflectorily elicited action on the gastroesophageal sphincter and the stomach. Carlson *et al.* (1922) studied the response of the gastroesophageal sphincter to mechanical stimulation of the biliary tract. The studies were made on decerebrated or anesthetized cats, and the effect was recorded by balloon. Mechanical stimulation of the gallbladder or the common duct was followed by a marked hypertension in the sphincter, in some cases lasting for fifteen minutes. Dey *et al.* (1946) using dogs, studied the effect of mechanical stimulation of the biliary tract on the length of the esophagus. Stimulation of the common duct, distension of the gallbladder or distension of the cystic duct resulted in a shortening.

Most studies, however, have concentrated on the effect on intragastric pressure and gastric motility, and mechanical and chemical stimulation of the biliary tract have been used (Barber and Stewart, 1920; Smith and Miller, 1929; Brush and Patterson, 1939; Nakayama and Mori, 1967; Wyatt, 1967; Ossipov, 1972). The results from these studies are at variance and the responses of the stomach were recorded as an increase as well as a decrease in intragastric pressure and motility.

These experiments demonstrate that it is possible reflectorily to elicit changes in intragastric and gastroesophageal sphincter pressure. However, for several reasons these results cannot directly be applied to the present material. The reaction in the stomach and the sphincter is not unambiguous, and the

stimuli used were of a character and intensity which cannot be paralleled to human physiology. It must therefore be regarded as unclarified whether the recorded abnormalities in sphincter pressure are mediated by reflexes.

In the light of our present knowledge of the control of sphincter pressure, an increase in serum gastrin will be the most likely explanation of a hormonally induced hypertensive sphincter. Serum gastrin has not been studied in patients with gallstones or the postcholecystectomy syndrome, and it is therefore impossible to validate or invalidate this possibility. It may be supposed, however, that in some cases these disorders will be accompanied by high serum gastrin levels conditioned by reflux of bile to the stomach. Capper, Butler, Kilby, and Gibson (1967) made radiological studies of the pylorus function in 18 patients with gallstones. Of these 18 patients, 14 had dyspepsia in addition to attacks of gallstone pain, and pyloric function was abnormal in all 14. Of four patients with pain only and no dyspepsia, the pyloric-regurgitation test was normal in two. It is suggested that the secondary symptoms of gallstones may be due to pyloric incompetence with regurgitation of duodenal contents. Johnson (1972) studied the pyloric function by means of a modified pyloric-regurgitation test. Regurgitation was assessed radiologically and biochemically, and the material included patients with gallstones and patients having previously undergone cholecystectomy. In both groups there was close correlation between a history of dyspepsia and the detection of pyloric regurgitation. In some patients with dyspepsia the symptoms actually occurred at the time of regurgitation. It is suggested that patients with a severely malfunctioning pylorus have symptoms which are little altered by cholecystectomy and that those patients, in whom the pyloric malfunction is in some way related to their gallstones, will be relieved by cholecystectomy.

These two studies demonstrate unambiguously that some patients with gallstones or the postcholecystectomy syndrome have an abnormal regurgitation of bile to the stomach. Bedi, Gillespie, and Gillespie (1968) showed that local application of bile salts in the antrum elicits acid secretion via a hormonal mechanism. The investigators conclude that contact between bile and the antrum elicits acid secretion via liberation of endogenous gastrin.

On the evidence of the results of these studies there is reason to suppose that, in some patients there are factors which condition an increased liberation of endogenous gastrin. A high serum gastrin level may therefore be the cause of the high pressure in patients with the postcholecystectomy syndrome and in some of the patients with gallstones. On this theory it has to be accepted that in some cases cholecystectomy reduces and in other elicits or accentuates the tendency to reflux of bile from the duodenum into the stomach.

The present findings allow the conclusion that in some cases hypertensive

sphincter may occur without concomitant symptoms. This conclusion is based on the fact, that of the 17 patients who had a hypertensive sphincter at follow-up after cholecystectomy, seven stated that they were in good health and without symptoms from the upper abdomen. It should be added that they were all checked within two to four months after the operation, and it can therefore not be excluded that the hypertensive sphincter is expressive of a predisposition and that these patients will develop symptoms at a later stage.

CHAPTER X

Hepatic vagotomy as a treatment in selected cases of hypertensive gastroesophageal sphincter

Introduction

Selective hepatic vagotomy has earlier been used in combination with cholecystectomy, and for the treatment of the postcholecystectomy syndrome (Mallet-Guy, 1949; Schein *et al.* 1969; Grassi, Sbuelz, and Dell'Osso, 1970; Iliescu, 1970). On the theory that a hypertensive gastroesophageal sphincter may be wholly or partly responsible for the symptoms, and secondary to pathophysiological changes in the biliary tract, resection of the hepatic rami was performed in a small and selected material.

Material

The material consists of seven patients, six women and one man, who were studied in the period December, 1970, to March, 1973. Ages varied from 32 to 68 years. It was a condition for acceptance in this series that the pre-operative radiological examination did not reveal hiatus hernia.

The stomach was intact in all patients, but six of them had previously undergone cholecystectomy.

The predominant symptom was pain across the upper abdomen with maximum in the epigastrium or under the right curvature. The intensity of pain varied in the individual patient and in the series as a whole but, all of them had regularly required painrelieving injections. In addition to pain, three patients had occasional attacks of dysphagia, characterized as a feeling of the food stopping up behind the lower part of the sternum. None of the patients complained of heartburn.

All patients had undergone radiological examination of the stomach and biliary tract. There were no evidence of gastric or duodenal ulcer, and stones were not demonstrable in the biliary tract.

Method

The *manometric studies* of the gastroesophageal sphincter were performed as described in chapter IV. These studies were carried out immediately before, and six to 11 months after operation.

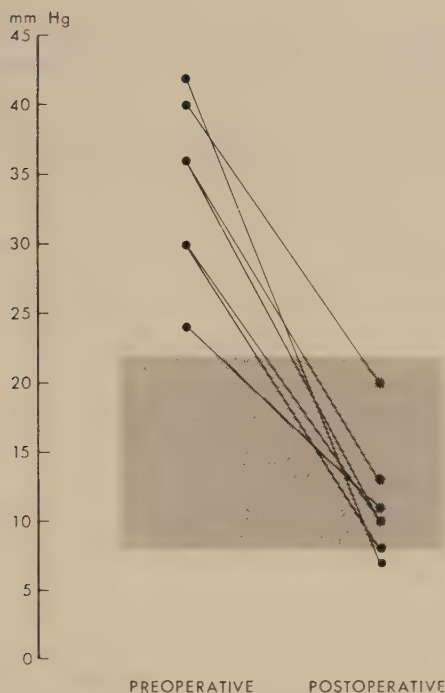


Fig. X-1. Each individual pre- and postoperative gastroesophageal sphincter pressure in relation to the normal area (hatched).

The *common duct pressure* was recorded in six of the seven patients, using a single catheter of the same type and with the same flow rate as that in the manometric studies of the gastroesophageal sphincter. A level of 10 cm above the couch was used as zero reference.

All operations were made with the intention to perform hepatic vagotomy.

Hepatic vagotomy was performed by resection, in omentum minus, of the branches from the anterior vagus towards the liver and biliary tract. One patient, in whom the biliary tract was intact and without stones, underwent simultaneous cholecystectomy. In one case the hiatus was felt to be wide, and the cardia was attached to the posterior wall of the abdomen, and the crurae were sutured in front of the esophagus.

Results

Fig. 1 shows the preoperative and postoperative sphincter pressures of each patient. Table I states the preoperative and postoperative sphincter pressures, as well as the intraoperative common duct pressures. The postoperative mean sphincter pressure is significantly lower than the preoperative mean

Case no.	Gastroesophageal sphincter pressure (mm Hg)		Intraoperative common duct pressure (mm Hg)	
	Preoperative	Postoperative	Before h.v.	After h.v.
1	24	11	—	—
2	40	20	9	6
3	30	8	47	18
4	30	10	13	13
5	42	7	35	35
6	36	10	13	13
7	36	13	18	18
Mean	34	11	23	17

Table X-I. Pre- and postoperative gastroesophageal sphincter pressure, and intraoperative common duct pressures.

($0.05 > p_w$). The postoperative mean is not different from the normal mean. There is no difference between mean common duct pressures before and after vagotomy. It was also investigated whether there might be a relationship of preoperative sphincter pressure to preoperative common duct pressure, and of the fall in sphincter pressure to changes in common duct pressure, but the coefficients of correlation are not significant.

Before operation there were no cases of spastic esophagus, but four patients had insufficient relaxation of the sphincter on swallowing. After operation there were no abnormalities.

In two patients symptoms persisted after the operation, whilst the remaining five were satisfied with the results, although they had not become free of pain. They had occasional attacks of pain of the same location as prior to operation, but the attacks did not occur so frequently, and the pain was less intense. None of the patients had noticed dysphagia. One patient had severe obstipation for a short while, but bowel function spontaneously returned to normal. None of the remaining patients had had changes in the frequency of defaecation.

Discussion

In the present material consisting of six patients with the postcholecystectomy syndrome, and one with dyspepsia, resection of the hepatic rami from the anterior vagus nerve resulted in a fall in mean sphincter pressure from

34 to 11 mm Hg. It is also evident from the results that the drop in sphincter pressure cannot be related to simultaneous changes in the common duct pressure.

The effect of this operation on sphincter pressure has not been studied previously, and the present material does not allow any conclusion with regard to the mechanism which elicit the reduction in pressure. It will be natural to seek the cause either in disruption of an afferent reflex pathway with effect on the sphincter, or in a secondary effect mediated by the changes in the stomach, biliary tract and liver entailing the resection. These two possibilities will be discussed in the following.

Several detailed anatomical investigations have been made of the distribution of the hepatic rami (McCrea, 1924; Alexander, 1940; Mitchell, 1940; Jackson, 1948; Royster, Sloan, McCain, and Shohl, 1949; Mester, 1953; Kjellgren, 1954; Burge, 1960; Ferguson, Billings, Swensen, and Hoover, 1960; Pritchard, Griffith, and Harkins, 1968; Loeweneck, 1971; Stelmasiak and Kurylcio, 1971). There is general agreement that a variable number of branches run from the anterior vagus nerve to the hilum of the liver. These fibres traverse the upper portion of the lesser omentum and, together with sympathetic fibres from the coeliac plexus form the anterior hepatic plexus. The branches from the hepatic plexus supply the liver, biliary tract, duodenum and pancreas. McCrea (1924) have described purely parasympathetic branches from the hepatic rami running towards the stomach and supplying the pylorus and antrum. This has later been confirmed by Franksson (1948), Jackson (1948), and Grassi *et al.* (1970).

As mentioned in chapter IX there is an anatomical and a physiological basis of afferent reflex activity from the liver and biliary tract, but there are only two reports on the activity in the hepatic rami (Nijijima, 1969; Nijijima, 1969a). He recorded afferent impulse discharge from a fine filament of a nerve dissected from the hepatic branches in guinea pig and found that the hepatic rami are afferent pathways for glucoreceptors and osmoreceptors in the liver parenchyma.

As mentioned in chapter IX there is reason to believe that there are tensionreceptors and chemoreceptors in the biliary tract, and it is probable that the hepatic rami act as afferent pathway. This theory is supported by studies of the course of the pathways of the reflectory activity from the biliary tract. Carlson *et al.* (1922) studied the effect of mechanical stimulation of the biliary tract on gastroesophageal sphincter pressure in decerebrated or anesthetized cats. In the intact animals mechanical stimulation of the gallbladder or the common duct was followed by a marked hypertension in the sphincter. The same reaction was obtained although in a diminished degree, after section of the vagus nerves. The mechanical stimulation was without effect after section of both vagus nerves and sphlan-

nic nerves. It is not mentioned on which level the vagotomy was performed. Schrager and Ivy (1928) recorded the effect of distension of the common duct on the clinical picture in dogs. After resection of the right splanchnic nerves it was still possible, as in intact animals, to elicit salivation and vomiting. After supradiaphragmatic vagotomy combined with resection of the left splanchnic nerves an increase in tension could not elicit this reaction. Davis, Hart, and Crain (1929), using the same experimental setup, found that increased tension in the common duct in intact animals was followed by salivation and vomiting. The same reflex could be elicited after resection of the right splanchnic nerves. The effect of vagotomy was not studied. Dey *et al.* (1946) used anesthetized dogs and found that mechanical stimulation of the common duct, distension of the gallbladder or cystic duct resulted in a shortening of the esophagus. This reflex could not be elicited after vagotomy or pretreatment with atropine. Sphincter pressures were not recorded, and it was not stated, on which level the vagotomy was performed. Watanabe (1954) studied the vomiting reflex in cats. Electrical stimulation of the biliary tract caused vomiting. These studies were repeated after various operations, including cervical vagotomy, resection of the splanchnic nerves, and transection of the spinal cord on various levels. On the evidence of the results it was concluded that both vagus nerves and the sympathetic nerves conduct the afferent impulses, but that the vagus nerves play the primary role. Otsuji (1955), using the same experimental setup, found also that electrical stimulation of the biliary tract elicited vomiting. Cats, in which the splanchnic nerves were bilaterally sectioned, easily vomited by the same intensity of stimulus. Electrical stimulation of the biliary tract in cats after cervical vagotomy could not induce vomiting. Nakayama and Mori (1967) studied the effect of distension of the common duct on intragastric pressure and gastric motility. These studies were made on anesthetized dogs, and it was found that in two out of three dogs the increase in tension was followed by an increase in the intragastric pressure and the amplitude of the contractions. After cervical vagotomy there was either no response or an inhibition.

These animal experiments demonstrate that intact vagus nerves are essential to the reflectorily elicited changes in the gastroesophageal sphincter and the stomach. However, the effect of resection of the hepatic rami on these reflexes has not been studied, and it is therefore not possible to draw any conclusions with regard to the importance of these branches as afferent pathways. It is evident, however, that after resection of the splanchnic nerves it is still possible to elicit an reflectory effect from the biliary tract on the stomach, and this means that the vagus nerves act as afferent pathways from the biliary tract. It is therefore possible that resection of the hepatic rami results in the non-occurrence of a reflectorily conditioned in-

crease in gastroesophageal sphincter pressure. The releasing stimulus is unknown, and in this context it should be mentioned that the pressure values recorded in the common duct, cannot be taken as an expression of the pressures in the basal state, because different kinds of anesthesia and drugs with effect on the autonomous nervous system have been used.

As previously mentioned, it is possible that the fall in gastroesophageal sphincter pressure is secondary and conditioned by the changes in the stomach, biliary tract and liver, which follow resection of the hepatic rami. The responses that are elicited in these organs will be discussed in the following.

Several authors have studied the importance of the hepatic rami to gastric motility and secretion in animals (Wohlrabe and Kelley, 1959; Stavney, Kato, Griffith, Nyhus, and Harkins, 1963; Legros, Shiina, and Griffith, 1968; Geist and Jones, 1971). The results demonstrate that it is not possible, on acute examinations, to demonstrate efferent activity in the hepatic rami with effect on gastric motility or acid secretion. However, these results are not in agreement with those reported by Amdrup and Griffith (1971). They studied the effect of selective hepatic vagotomy on gastric and small bowel emptying. These studies were made on dogs, and the effect was assessed by radiological examination eight weeks after the operation. Hepatic vagotomy was found to be followed by delayed emptying of the stomach and small bowel. The most likely cause of this difference in results must be that in the last mentioned work it is the question of experiments with a longer time of observation.

The function of the hepatic rami as efferent pathway for the biliary tract has been studied several times. Animal experiments have focussed on the effect of peripheral electrical stimulation or resection on pressures and electrical activity in the biliary tract (Mester and Johasz, 1956; Stavney *et al.* 1963; Watts and Dunphy, 1966; Schein *et al.* 1969; Hopton and White, 1971; Nana, Mireioiv, Neumann, and Nana, 1971; Satler, Sakakihara, Nusbaum, and Tumen, 1972; Loeweneck, Brükner, and Rux, 1973). The human investigations have centred on the effect on the resistance of the sphincter Oddi and the clinical picture (Schein *et al.* 1969; Grassi *et al.* 1970; Iliescu, 1970). It is the general view that efferent impulses, conducted through the hepatic rami, contribute to the maintenance of the tone in the biliary tract, and that resection of these branches is followed by a reduction in the resistance of the sphincter Oddi. This is a common feature in human studies, and it is therefore remarkable that it could not be demonstrated in the present material. On the other hand, this material is very small and my experience in recording pressure in the biliary tract reduces itself to the cases reported.

The hepatic rami constitute the efferent vagal innervation of the liver, and

animal experiments have demonstrated that resection is followed by metabolic changes in the liver parenchyma. Amdrup and Griffith (1970), Amdrup and Griffith (1971) and Geist and Jones (1971) have demonstrated that this operation is followed by changes in the qualitative characteristics of the hepatic bile, and by a reduction in the capacity of the liver to excrete alien substances.

This review of the functions which the hepatic rami have as efferent parasympathetic nerves, leads to the conclusion that the reduction in gastroesophageal sphincter pressure may be secondary. It has been demonstrated that resection of the hepatic rami in dogs is followed by a reduction in the rate of emptying of the stomach (Amdrup and Griffith, 1971). The gastroesophageal sphincter is closely related to the motility of the stomach, and it is therefore possible that the fall in sphincter pressure is the consequence of a decrease in the muscular tension of the stomach. Another possibility is a secondary effect via the changes that are induced in the external biliary tract. Hepatic vagotomy in man results in a raised threshold of pain to an artificially induced rise in pressure (Schein *et al.* 1969). This means that the sensitivity of the pain receptors decreases, and it is possible that the same applies to receptors with reflectory action on the gastroesophageal sphincter via the sympatic nervous system, or via the coeliac ramus from the posterior vagus nerve.

The clinical results must be regarded as poor. The operation had no effect at all on the symptoms in two of the seven patients, and in the remaining five the symptoms persisted although they were not so intense and did not occur so often as before the operation. It may be concluded that, as a treatment of selected cases of hypertensive sphincter, hepatic vagotomy at best results in a reduction of the intensity of the symptoms. On the basis of the combination, – unchanged or slightly improved symptomatology and an unambiguous reduction of sphincter pressure –, it may also be concluded that in the present material, the hypertensive sphincter was without relation to, or only partly responsible for the preoperative symptoms.

Concluding remarks

For measuring of pressures in the gastroesophageal sphincter and the corpus of the esophagus there are several methods to choose between. Each method has its advantages, and it is therefore necessary, before making one's choice, to know exactly what it is one wishes to measure.

The aim of the present work has been to record sphincter pressures, and for this purpose the choice fell on waterfilled polyethylene catheters with a constant flow, and a flow rate that was low enough not to induce changes in the milieu of the stomach. A disadvantage to this method is that it is not possible to record rapid variations in pressure. The method gives a reliable recording of fundic pressure, resting sphincter pressure, fall in sphincter pressure on swallowing and resting pressure in the corpus of the esophagus, but is unsuitable for recording of the duration of sphincter relaxation and the amplitude of peristaltic contractions in the corpus of the esophagus.

With this method the gastroesophageal sphincter pressure can be reproduced with a coefficient of variation of 0.12 to 0.14. By employing a system of catheters, where two of the side-holes are situated on the same level but have different radial orientation, the pressure values recorded will in some cases be different. The difference is slight and not systematic, and it is not the same catheter which constantly records a value that is either higher or lower than that recorded by the other catheter. However, there are differences, and it is possible that a better reproducibility can be achieved by using a single catheter with more side-holes on the same level.

Studies carried out in recent years have clearly documented that both neurogenic and hormonal factors are involved in the normal control of sphincter pressure. With regard to the neurogenic factors, the results of *in-vitro* investigations are well in keeping with the recordings of sphincter pressures *in-vivo*. *In-vitro*, stimulation of cholinergic and alpha-adrenergic receptors has been found to elicit contraction; *in-vivo*, the result is a rise in sphincter pressure. *In-vitro*, stimulation of the beta-adrenergic receptors elicits relaxation and *in-vivo*, the result is a fall in sphincter pressure.

The same agreement has been found between *in-vitro* and *in-vivo* studies of the effect of gastrin. *In-vitro*, gastrin produces contraction of

muscle in the sphincter area, and *in-vivo*, injection of gastrin or penta-gastrin is followed by a rise in pressure. It is characteristic of the *in-vivo* effect of gastrin that it can be produced with a dose which is smaller than that required to obtain maximum effect on the parietal cells. In this connection it is of interest that intragastric instillation of alkali is followed by an increase in sphincter pressure.

According to the above mentioned characteristics the effect of gastrin may be accepted as physiological. It can be produced with a dose smaller than that required to obtain maximum effect on the parietal cells, and it can be reproduced by procedures promoting the liberation of endogenous gastrin. Yet it is not quite clear whether fulfilment of these two conditions suffices, and considerable caution is advised in drawing conclusions with regard to the interrelationship between serum gastrin and sphincter pressure. One of the reasons for this is that comparative studies have not been made of, on one hand – serum gastrin after administration of different doses of exogenous gastrin and, on the other – serum gastrin in pathophysiological states in the gastrointestinal tract. The question of a relationship between serum gastrin level and sphincter pressure is of great interest. When constructing dose-response curves for exogenous gastrin and sphincter pressure many investigators have used rapid intravenous injection of gastrin, and it is very likely that this procedure has induced transitory and very high rises in serum gastrin. This problem is also evident from the results published by Frank *et al.* (1973) who investigated the effect of continuous pentagastrin infusion on sphincter pressure in normal human subjects. They administered two different doses of pentagastrin, 0.015 and 0.025 $\mu\text{g}/\text{kg}$ per min, respectively, and gastric acid secretion was constantly removed during the study. The lower dose resulted in a maximum rise in sphincter pressure from 19 to 24 mm Hg. With the higher dose pressure increased from 21 to 29 mm Hg. After 1 hr of continuous infusion an intravenous bolus of 0.5 $\mu\text{g}/\text{kg}$ of pentagastrin was injected. This resulted in a rise in both series, to 39 and 45 mm Hg, respectively. The authors concluded that constant infusion of pentagastrin in doses, which maximally stimulate gastric acid secretion, is followed by a modest increase in sphincter pressure, and that consistently elevated levels of pentagastrin have less effect on sphincter pressure than an intravenous bolus of the hormone.

Another reason for exercising considerable caution in drawing direct comparison between serum gastrin and sphincter pressure is that there are studies which demonstrate that patients with pernicious anemia and patients with the Zollinger-Ellison syndrome may have a normal sphincter pressure. Isenberg, Csendes, and Walsh (1971) made simultaneous recordings of sphincter pressure and serum gastrin in normal subjects, in three patients with pernicious anemia and in five patients with the Zollinger-Ellison syndrome.

For the three groups mean sphincter pressure was 13.3, 13.9 and 22.2, respectively. In both patient groups serum gastrin levels were substantially raised, and as a possible explanation of the differences in sphincter pressure it is suggested that the biological activity of the circulating gastrin in the Zollinger-Ellison syndrome may differ from that in the patients with pernicious anemia. Siewert, Jennewein, Arnold, and Creutzfeld (1973) studies serum gastrin and sphincter pressure in five patients with the Zollinger-Ellison syndrome. In all patients sphincter pressure was normal and the serum gastrin level appreciably elevated. The authors opine that the normal pressure is the result of the sphincter's adapting to a high serum gastrin level. The fact that rapid intravenous injection of pentagastrin led to a minor rise in pressure in patients than in normal subjects is in support of this view.

These results demonstrate that patients with a high serum gastrin need not necessarily have a high sphincter pressure. In this connection it should be borne in mind that gastrin is not the only gastrointestinal hormone with effect on the sphincter pressure. Cohen and Lipshutz (1971) and Jennewein *et al.* (1973) showed that exogenous secretin or intraduodenal instillation of hydrochloric acid inhibits the gastrin-stimulated sphincter. This means that a rise in the serum secretin level can eliminate or reduce the effect of an increase in serum gastrin. This may account for the normal pressure in some of the patients with the Zollinger-Ellison syndrome. In the present state of our knowledge of the factors which condition liberation of endogenous secretin, it is unlikely that the same mechanism should be held responsible for the normal pressure in pernicious anemia.

The above mentioned studies are the only ones in which simultaneous recordings have been made of serum gastrin and sphincter pressure. There are no investigations documenting that a low pressure is attributable to a low serum gastrin level, but attempts have been made at proving this indirectly. Rosenberg and Harris (1971) demonstrated that patients with "clinical gastroesophageal reflux" have dose-response curves for the action of pentagastrin on sphincter pressure of the same shape and with the same per cent increase in sphincter pressure as normals, but twice as much pentagastrin was required to obtain peak response. The gastric acid dose-response curves also had the same shape in the two groups, but the acid output was only about half the normal at each dose in the patient group. It was concluded that low sphincter pressures are secondary and conditioned by decreased stimulation of endogenous gastrin. Lipshutz *et al.* (1973) also found that the per cent change in pressure in response to exogenous pentagastrin was similar in patients with reflux and normals. The per cent change in pressure in response to endogenous stimulation by gastric deacidification was significantly lower in the reflux group. The results of the present investigation are not in support of these conclusions. It is not possible to demonstrate a rela-

tionship between maximum acid secretion and sphincter pressure in any of the ulcer groups.

In case of a direct relationship between serum gastrin and sphincter pressure it is to be expected that distal resection of the stomach will be followed by a low pressure. It is consistent with this expectation that in patients having undergone complete vagotomy and resection the mean pressure is lower than in patients who have undergone complete vagotomy and pyloroplasty and lower than in normals. As regards sphincter pressure after resection without vagotomy the results are not consistent with the analyses of serum gastrin. Stadil and Rehfeld (1972) demonstrated that this operation is followed by a fall in serum gastrin to about half of the normal level, but in the present material only patients in good health had a low pressure. Patients with sequels without any known organic cause had a mean pressure that is higher than in normal subjects, and in a series of 22 patients it was not possible to demonstrate a difference in mean sphincter pressure before and after resection of the stomach without vagotomy.

It appears from the above that the pathophysiological mechanisms of a low pressure remains obscure. A major cause of this is that sphincter pressure and serum gastrin have not been studied simultaneously in larger materials. It may be concluded that it has not been proved that a low sphincter pressure is attributable to a low serum gastrin level, and there is no indication that a reduction in serum gastrin will necessarily be followed by a fall in sphincter pressure.

As regards the opposite extreme – the hypertensive sphincter – the pathophysiological mechanisms are also unclarified. On the evidence of the findings in the previously mentioned studies of patients with pernicious anemia or the Zollinger-Ellison syndrome, it may be concluded that an abnormally high serum gastrin level is not inevitably followed by a high sphincter pressure. Hypertensive sphincter occurs in all subgroups of the present material, and from a pathophysiological view it is noteworthy that it is most frequent in patients with sequels after resection without vagotomy and in patients with the postcholecystectomy syndrome. Serum gastrin has not yet been studied in the latter group but other investigators have demonstrated low serum gastrin in patients with resection of the stomach. It may therefore be supposed that a hypertensive sphincter can be elicited by other factors, and it will be natural to seek the cause in a reflectorily induced hypertension.

Animal experiments are in support of the theory that a hypertensive sphincter can be elicited via reflexes from the stomach. Titchen and Wheeler (1971) demonstrated that electrical stimulation of the central ends of the vagus nerves, cut in the abdomen, elicit an increase in sphincter pressure, and several authors have demonstrated that mechanical stimulation of the stomach results in an increase in sphincter pressure (Carlson *et al.* 1922;

Clark and Vane, 1961; Titchen and Wheeler, 1971). Diamant and Akin (1972) found a marked increase in sphincter pressure in conjunction with pressure increase in the upper part of the stomach, and the changes in sphincter pressure were closely related to changes in intragastric pressure in a ratio of 8:1. It is mentioned in this work that truncal vagotomy abolishes the pressure response to increases in intragastric pressure.

On the theory of reflectorily elicited hypertension, the mucosal changes observed on gastroscopy have to be accepted as being the factor which, either direct or by altering muscle tension, elicits a pressure increase in the gastroesophageal sphincter. It is in keeping with this theory that patients with sequels after complete vagotomy and resection have a lower mean pressure than those with sequels after resection without vagotomy.

Likewise there are animal experiments which seem to show that hypertension in the gastroesophageal sphincter may be elicited reflectorily from the biliary tract. Carlson *et al.* (1922) demonstrated that mechanical stimulation of the external biliary tract is followed by a marked hypertension in the sphincter. Dey *et al.* (1946) found that the same stimulus elicited contraction of the longitudinal musculature in the esophagus. These results demonstrate a reflectory influence on the esophagus from the biliary tract, and in the first mentioned study a pronounced increase in pressure was recorded directly. If one applies the results of these animal experiments to the present material of patients with the postcholecystectomy syndrome and accepts the theory of reflectorily elicited hypertension, it must be admitted that the eliciting stimulus is unknown. Resection of the hepatic rami in patients with the postcholecystectomy syndrome and hypertensive sphincter was in all cases followed by a reduction in pressure. This result supports the theory of a reflectorily elicited hypertension. However, due to the many different afferent and efferent functions of the hepatic rami the results cannot be accepted as a final proof.

As will appear from the above, the pathophysiology of hypotensive and hypertensive sphincters is unclarified and it is in direct consequence thereof that the clinical value of the manometric study is limited. It is possible to make a classification on the basis of sphincter pressure but from this it does not necessarily follow that an abnormal sphincter pressure is solely or partly responsible for the clinical picture. Abnormal pressures may occur in patients with organic diseases, ulcers or gallstones, but larger materials are required to determine whether the combination of organic disorders in the stomach or biliary tract and an abnormal sphincter pressure indicates a therapy other than that usually employed.

The above mentioned problem is more obvious in patients with dyspepsia without organic cause and in patients with hiatus hernia. For the first mentioned group an abnormal pressure will be the only positive finding, and for

the second group it is widely held that the hiatus hernia is of minor importance and the abnormal sphincter pressure the real cause of the symptoms. In the literature there is a clear tendency to conclude direct from the results of the manometric study to the clinical picture. Hypotensive sphincter is interpreted as tantamount to reflux, and the symptoms as the results of a contact between gastric contents and the esophageal mucosa. Hypertensive sphincter is regarded as a disease entity *per se* and directly responsible for the symptoms. However, these assertions have not been substantiated, and in the following I shall discuss the reservations that have to be made with regard to conclusions based on recording of the resting gastroesophageal sphincter pressure only.

Cohen and Harris (1970) demonstrated that there is a close relation between sphincter pressure and the resistance on passage from the stomach through the gastroesophageal sphincter and into the corpus of the esophagus. This means that patients with low pressures are prone to reflux, and the present as well as previous reports demonstrate that patients with heartburn have a low mean sphincter pressure. It should be emphasized, however, that this separation between, on one hand – patients with heartburn, on the other – normal subjects and patients without heartburn is not complete but that there is an appreciable overlapping. Many patients with heartburn have a normal pressure, and there are patient without heartburn who have a pressure below the lower limit of normal. The principal reason for this overlapping are differences in the quantitative and qualitative characteristics of gastric contents, and individual differences in the sensitivity of the esophageal mucosa. Furthermore, it should be borne in mind that the sphincter is not a static but a dynamic structure which changes its pressure spontaneously, in connection with changes in intragastric pressure and in relation to food intake. The resting pressure may therefore be regarded as a snapshot of the pressure conditions.

It is well established that heartburn is caused by contact between gastric contents and the esophageal mucosa, and from a pathophysiological point of view it is therefore of interest to learn that these patients have a low pressure. From a clinical point of view, however, it will be more relevant to clarify whether a certain complex of symptoms, with or without heartburn, may be ascribed to reflux. A clarification of this problem will require supplementary diagnostic investigations, including determination of basal and stimulated gastric secretion, continuous recording of pH in the lower part of the esophagus and acid perfusion of the esophagus. Such a series of investigations will render it possible, in each individual case, to answer the crucial questions – does the stomach contain acid in such quantities and of such an acidity that reflux may be supposed to elicit pathological changes? – does reflux occur more frequently than in normal subjects? and – can

acid perfusion of the esophagus reproduce part of or the entire spontaneous complex of symptoms? A programme adding these investigations to the routine examinations is very comprehensive, and it would therefore be expedient if, on the basis of the resting sphincter pressure, those patients could be sorted out in whom a so comprehensive diagnostic programme would be superfluous. Reflux can be expected to be rare in patients with sphincter pressure above 15 mm Hg, but to obtain the final proof it will be necessary to carry out all investigations in all the patients of a representative material.

Several investigators have accepted that the hypertensive sphincter can be the direct cause of pain, but the proof is based on a small material only (Ellis *et al.* 1964). These investigators reported the results of myotomy in the sphincter area in six cases of hypertensive sphincter without spastic esophagus. Preoperatively, the symptoms were pain in two cases, pain and dysphagia in three and dysphagia in one. The results were stated to be excellent or good in four, fair in one and poor in one. From this it is obvious that, in some cases, the hypertensive sphincter must be a disease entity *per se* presenting symptoms. However, if the results of the present study are combined with those of other studies, it is possible to adduce examples illustrating that in some cases the hypertensive sphincter does not present symptoms and that in others it is only partly responsible for the symptoms. Such examples will be given in the following.

Hypertensive sphincter can be induced by drugs without being accompanied by symptoms. This is documented by the fact that injection of cholinergic agents or pentagastrin is followed by a rise in normal sphincter pressure of 300 to 400 per cent. This pressure increase does not produce pain or other symptoms.

Hypertensive sphincter can occur spontaneously without concomitant symptoms. This is evident from the present study of the effect of cholecystectomy on sphincter pressure. Of the 17 patients who had a hypertensive sphincter at follow-up after cholecystectomy, seven stated that they were in good health and without symptoms from the upper abdomen. It should be added that the period of observation is short, two to four months, but it may be concluded that a hypertensive sphincter is not inevitably accompanied by symptoms. The time of observation being short, it cannot be excluded that the high sphincter pressure expresses a predisposition and that after a longer time of observation these patients will develop symptoms.

Hepatic vagotomy will in some cases of hypertensive sphincter result in a fall in pressure but this is not tantamount to disappearance of the pre-operative symptoms. This is evident from the present material, in which resection of the hepatic rami was performed in seven patients, six of whom had a postcholecystectomy syndrome. After operation the pressure was below the upper limit of normal in all cases but two patients stated that

their symptoms have remained unchanged, and the remaining five had still symptoms although less intense. The result allows the conclusion that the hypertensive sphincter cannot have been solely responsible for the preoperative symptoms. It is possible that in five cases the preoperative symptoms could to some degree be ascribed to the high pressure.

In the present state of knowledge there is reason to believe that there are three types of hypertensive sphincter. One, in which it is a disease entity *per se*, accompanied by symptoms; another, in which it is a more or less important part of a greater pathophysiological entity and thus without relation to or only partly responsible for the symptoms; and a third which is without concomitant symptoms and therefore without clinical interest.

The clinical value of the diagnosis hypertensive sphincter is reduced in that the symptom-presenting cases cannot be classed with any of the two first mentioned types. Effective therapy would involve myotomy in the sphincter area. This implies a risk in itself, as myotomy means total elimination of the contribution of the sphincter to the antireflux mechanism. Reflux might therefore be the result and with it a new pathological state which, at worst, might prove refractory to treatment. This risk would be acceptable if one could with reasonable certainty separate the cases in which hypertensive sphincter was the direct cause of the symptoms. Since this cannot be done it must be considered inadvisable to use myotomy in the treatment of hypertensive sphincter.

The aim of this review has been to stress the reservations which have to be made with regard to conclusions based solely on the recording of resting gastroesophageal sphincter pressure. The greatest obstacle to a relevant clinical use of manometry is that the pathophysiological mechanisms involved in an abnormal sphincter pressure have not been fully elucidated. In recent years research has contributed appreciable to a better understanding of the neurogenic and hormonal regulation of the normal sphincter pressure but this does not mean that it is possible to give an unambiguous explanation of the pathophysiological mechanisms involved in an abnormal pressure. Future research will therefore be charged with the task of clarifying the relations between the factors responsible for the normal physiological regulation and those active under pathophysiological conditions.

Summary

CHAPTER I

The aim of the present work has been to elucidate the relationship between gastroesophageal sphincter pressure and different factors with origin in the stomach, duodenum and biliary tract. With this in view a study has been made of the manometric characteristics of the gastroesophageal sphincter in normal subjects as well as in patients before and after operation for generally occurring organic and non-organic diseases of the upper abdomen.

CHAPTER II

A review of the technical problems involved by using perfused catheters for recording of gastroesophageal sphincter pressures and pressure variations in the corpus of the esophagus. On the evidence of the results of model studies three conclusions are drawn: reliable pressure recording requires a constant flow, – the flow rate is of no consequence for pressures recorded at slow variations in pressure and – recordings of rapid variations in pressure requires a high flow rate.

In-vivo investigations have confirmed these conclusions. With stepwise withdrawal from the stomach through the gastroesophageal sphincter and into the corpus of the esophagus the variations in pressure are slow, and the flow rate therefore of no consequence. As an example of rapid pressure variations requiring a high flow rate is mentioned the peristaltic waves in the esophagus.

The purpose of the present work has been to record the resting gastroesophageal sphincter pressure, and a low flow rate has been chosen for two reasons: it does not elicit disturbing secondary peristalsis, and it allows protracted pressure recordings without inducing any greater changes in the intragastric milieu. These advantages are gained to the disregard of other parameters. Thus it is possible to obtain reliable recordings of fundic pressure, sphincter pressure, sphincter relaxation on swallowing and basal pressure in the corpus of the esophagus, but the flow rate used is not high enough for accurate recording of the duration of sphincter relaxation,

and the amplitude of the peristaltic contractions of the corpus of the esophagus.

CHAPTER III

In recent years it has been demonstrated that both neurogenic and hormonal factors are involved in the physiological regulation of the gastroesophageal sphincter pressure.

In-vitro studies of circular muscle from the sphincter area have shown that drugs with stimulating effect on the cholinergic and alpha-adrenergic receptors produce contractions, whilst drugs stimulating the beta-adrenergic receptors elicit relaxation. These results are well in keeping with those obtained by recording of sphincter pressures after injection of agents acting on the autonomous nervous system.

In-vitro, gastrin elicits contraction of circular muscle from the sphincter area, and *in-vivo*, injection of gastrin or pentagastrin is followed by a rise in gastroesophageal sphincter pressure. This rise can be elicited with doses smaller than that required to obtain the maximum effect of gastrin on the parietal cells, and it can be reproduced by procedures promoting the liberation of endogenous gastrin. In animal experiments injection of gastrin antiserum is followed by a gradual fall in sphincter pressure. These results allow the conclusion that serum gastrin is an important factor in the physiological control of sphincter pressure and essential to the maintenance of the normal resting pressure.

CHAPTER IV

Initially a description is given of the apparatus and method used. Next the characteristics of normal and abnormal types of curve are mentioned and illustrated, and the criteria according to which the patient material has been selected are described. The chapter winds up with a characteristic of the various parameters for the normal material and with a review of studies on reproduction of the gastroesophageal sphincter pressure.

The discussion focusses on three subjects, – the technical problems associated with recording of the gastroesophageal sphincter pressure and the pressure in the corpus of the esophagus, – a comparison between the present and previously published normal materials and – interpretation of the different abnormalities in the curve pattern.

It is concluded that the apparatus and method used in the present study allow reliable recording of fundic pressure, gastroesophageal sphincter pressure, sphincter relaxation and basal pressure in the corpus of the esophagus. Since the system cannot record rapid variations in pressure it is unsuitable

for recording of the duration of sphincter relaxation, and the changes in pressure that are induced in the corpus of the esophagus on swallowing. Furthermore, it is concluded that the differences between the published normal materials are attributable to differences in the selection of the material, in the reading of the curves, in the construction of the pressure probes, and in the ways in which the studies are carried out. It remains obscure whether such abnormalities in the curve pattern as "double peak of pressure" and "double respiratory reversal" may occur under normal anatomical conditions or whether they are conditioned by deviations from the normal anatomy of the gastroesophageal region.

CHAPTER V

In a series of 98 patients with dyspepsia without any organic cause sphincter pressures are distributed both within and outside the limits of normal. In 54 patients the pressure was of the same magnitude as in normal subjects, whilst in 17 it was below and in 27 above the lower and upper limits of normal, respectively.

In patients with heartburn the mean sphincter pressure is lower than in normal subjects. There is, however, an appreciable overlapping between the two distributions.

In 23 patients with periodic dysphagia the mean sphincter pressure is higher than in normal subjects. Compared to patients without dysphagia, patients with dysphagia had a more frequent occurrence of abnormalities in the relaxation of the sphincter and the motility of the corpus of the esophagus.

The discussion falls in three parts. The first deals with the relationship between sphincter pressure and reflux, and the pathophysiological mechanisms behind a low pressure. It is concluded that brief recordings of sphincter pressure cannot be used to elucidate whether a clinical picture, entirely or partly, may be ascribed to reflux. In the case of low pressure there is reason to believe that, in some instances, low serum gastrin may be the cause, but there is no direct proof thereof. The second part deals with the clinical picture of hypertensive sphincter. It is emphasized that in some cases hypertensive sphincter has to be accepted as a symptom-presenting disease entity *per se*.

The third part deals with the relationship between the presence of dysphagia and the occurrence of abnormalities in the relaxation of the sphincter and the motility of the corpus of the esophagus.

CHAPTER VI

Manometric and clinical studies were made of 73 patients with hiatus hernia of the sliding type. Sphincter pressure was below the lower limit of normal

in 34 patients, within normal range in 28, and above the upper limit of normal in 11. In the group of patients with heartburn or heartburn and pain, and in the group of patients with heartburn and dysphagia or pain, heartburn, and dysphagia, the mean sphincter pressure is lower than in normal subjects. However, there is a considerable overlapping between these two groups and the group of normals. Patients with dysphagia or pain and dysphagia had a mean pressure which is not significantly different from the normal mean.

The results are compared with those previously reported, and analysed in relation to investigations of the dependence of sphincter function on the location of the sphincter.

It is concluded that manometry is important as a supplementary test in patients with hiatus hernia. In cases of low pressure the results should be taken as a guidance and an indication for further diagnostic examinations in order to clarify the relation between reflux and symptoms. In cases of hypertensive sphincter or spastic esophagus the manometric study is decisive for the diagnosis.

CHAPTER VII

Gastroesophageal sphincter pressure was studied in a material including 56 patients with duodenal ulcer, 12 with prepyloric ulcer, and 14 with gastric ulcer. In patients with duodenal ulcer the mean pressure is lower than in normal subjects. For the other groups the mean pressures are of the same magnitude as in normals. In patients with duodenal ulcer the mean pressure is lower in those with heartburn than in those without. There is no relationship, in any of the groups, between sphincter pressure and basal or stimulated acid secretion, respectively.

The discussion concentrates on the pathophysiological mechanisms behind the low pressure in duodenal ulcer. The possible causes are argued, – changes in serum gastrin, – changes in intragastric milieu, and – direct inhibitory impulses via the vagus nerves.

It is concluded that a low serum gastrin level is unlikely to be the cause. Nor is it possible to adduce evidence that an increase in basal acid secretion is able reflectorily to elicit a fall in sphincter pressure. The most likely explanation is that direct inhibitory impulses, transmitted to the sphincter via the vagus nerves, are part of the pathophysiological complex in duodenal ulcer.

CHAPTER VIII

The results of a study of sphincter pressure in patients after different types of gastric surgery are presented. After complete truncal vagotomy and pyloro-

plasty the mean pressure is of the same magnitude as in normal subjects. After complete truncal vagotomy and distal resection it is lower than after complete truncal vagotomy and pyloroplasty and also lower than in normal subjects. Following distal resection without vagotomy patients in good health had a lower mean pressure than normal subjects. Patients with sequels without any known organic cause had a mean pressure which is higher than that in normal subjects and higher than that in patients in good health after the same operation.

In 22 patients, on whom distal resection without vagotomy was performed, the postoperative mean pressure is not different from the preoperative mean.

The results are discussed in relation to our present knowledge of the neurogenic and hormonal control of sphincter pressure. In addition, mention is made of the receptors in the stomach and the function of the vagus nerves as afferent pathway for reflexes from the stomach to the gastroesophageal sphincter.

It is concluded that the results in patients who have undergone vagotomy and pyloroplasty, or vagotomy and resection, are consistent with the current view of the relationship between serum gastrin and sphincter pressure. The high pressure in patients with sequels after resection without vagotomy cannot be explained as the result of surgically induced changes in serum gastrin. The more likely explanation is that the high pressure is resulting from reflectorily mediated increase in gastroesophageal sphincter tension.

CHAPTER IX

This chapter presents the results from a study of gastroesophageal sphincter pressure in patients with diseases of the biliary tract, and the results from a study of the effect of cholecystectomy on sphincter pressure.

In a material of 121 cases of operatively verified gallstones mean sphincter pressure is not different from the normal mean. However, 16 had a pressure which is lower than the lower limit of normals and 28 had a pressure which is higher than the upper limit of normals.

In a group of 74 patients with operatively verified gallstones the mean postoperative pressure is not different from the preoperative mean.

In a material of 35 patients with the postcholecystectomy syndrome without hiatus hernia the mean pressure is higher than in normal subjects.

The discussion falls into two parts and concentrates on the possible causes of the recorded abnormalities in sphincter pressure. The first part deals with reflectorily elicited changes in sphincter pressure, and reviews the anatomical and physiological basis of an afferent reflex activity from the biliary tract to the gastroesophageal sphincter and the stomach.

In the second part mention is made of studies on pathophysiological conditions in the biliary tract as the cause of changes in serum gastrin.

With support in previously reported results it is possible to adduce arguments in favor of the theory that pathophysiological conditions in the biliary tract may give rise to both reflectorily and hormonally elicited changes in sphincter pressure. Further clarification would, however, require a more extensive diagnostic apparatus than the one used in the present study.

It is concluded that the hypertensive sphincter may occur in individuals who have previously undergone cholecystectomy but who, at the time of re-examination, are without symptoms from the upper abdomen. Therefore it has to be accepted that in some cases hypertensive sphincter may occur without concomitant symptoms.

CHAPTER X

This chapter reports the results of hepatic vagotomy as a treatment in selected cases of hypertensive gastroesophageal sphincter. The material comprised seven patients, six with the postcholecystectomy syndrome, and one with dyspepsia. Hepatic vagotomy resulted in a fall in sphincter pressure in all patients, and a fall in mean sphincter pressure from 34 to 11 mm Hg. The operation was without effect on intraoperative common duct pressure. There is no correlation between the fall in sphincter pressure and the intraoperative changes in common duct pressure.

The factors eliciting the fall in sphincter pressure are unknown, but the possible modes of action are discussed.

The clinical result was poor. Two patients stated that the operation was without any effect on their symptoms, and in the remaining five patients the preoperative symptoms persisted, although they were less intense.

It is concluded that the hypertensive gastroesophageal sphincter, in the present material, was without relation to, or only partly responsible for the preoperative symptoms.

CHAPTER XI

This chapter reviews the conclusions that may be drawn on the evidence of the results from the various subgroups of the total material.

Danish summary

KAPITEL I

Det anføres, at formålet med den foreliggende undersøgelse har været at belyse relationen mellem det gastro-oesophageale sphinctertryk og forskellige faktorer med oprindelse i ventriklen, duodenum og galdevejene. For at opfylde dette formål er der foretaget en undersøgelse over de manometriske karakteristika i den gastro-oesophageale sphincter såvel hos normale som patienter før og efter operation for almindeligt forekommende organiske og ikke-organiske sygdomme i øvre abdomen.

KAPITEL II

Der foretages en gennemgang af de tekniske problemer i forbindelse med anvendelse af perfunderede katetre til registrering af det gastro-oesophageale sphinctertryk og trykvariationerne i corpus oesophagei. På basis af resultaterne fra modelundersøgelserne kan der udledes tre konklusioner. For det første, – anvendelse af et konstant flow er en nødvendig forudsætning for en pålidelig registrering af trykket, for det andet, – ved langsomme trykvariationer er flowhastigheden uden indflydelse på det tryk som registreres, og for det tredje, – registrering af hurtige trykvariationer kræver en høj flowhastighed.

Konklusionerne fra modelundersøgelserne er efterprøvet *in-vivo*, og de har vist sig at være korrekte. Ved en trinvis tilbagetrækning fra ventriklen, gennem den gastro-oesophageale sphincter og op i corpus oesophagei, vil registreringen af sphinctertrykket få karakter af en langsom trykvariation, og flowhastigheden vil derfor ikke være af afgørende betydning. Som eksempel på hurtige trykvariationer kan nævnes den peristaltiske bølge i oesophagus, og en pålidelig registrering af amplituden vil nødvendiggøre en høj flowhastighed.

I det foreliggende arbejde har det været hensigten at registrere det basale gastro-oesophageale sphinctertryk, og der er anvendt et lavt flow. Valget af et lavt flow er begrundet i to hensyn. Et lavt flow udløser ikke forstyrrende sekundær peristaltik, og det er muligt at foretage længerevarende registrering

af trykket, uden at inducere væsentlige ændringer i det intragastriske milieu. Man må imidlertid erindre, at det, for at opnå disse fordele, må accepteres, at nogle af de øvrige parametre ikke kan anvendes i beregningerne. Der opnås en pålidelig registrering af trykket i fundus, trykket i den gastro-oesophageale sphincter, sphincterens relaxation ved synkning og det basale tryk i corpus oesophagei, men flowhastigheden er ikke tilstrækkelig til en nøjagtig registrering af varigheden af sphincterens relaxation og amplituden af de peristaltiske kontraktioner i corpus oesophagei.

KAPITEL III

Resultater fra de senere år har demonstreret, at den fysiologiske regulation af det gastro-oesophageale sphinctertryk udøves via såvel neurogene som hormonale faktorer.

Ved *in-vitro* undersøgelser af cirkulær muskulatur fra sphinctreområdet er det påvist, at farmaka med stimulerende effekt på cholinerge og alpha-adrenerge receptorer udløser kontraktion. Farmaka med stimulerende effekt på beta-adrenerge receptorer udløser relaxation. Der er god overensstemmelse mellem disse resultater og de resultater, som er opnået ved registrering af sphinctertrykket i relation til injektion af farmaka med effekt på det autonome nervesystem.

Ved *in-vitro* undersøgelser udløser gastrin kontraktion af cirkulær muskulatur fra sphincterområdet, og injektion af gastrin eller pentagastrin følges i *in-vivo* undersøgelser af en forøgelse af det gastro-oesophageale sphinctertryk. Denne forøgelse af sphinctertrykket kan registreres med doser, som er mindre end den dosis der er nødvendig for en maksimal effekt af gastrin på parietalcellerne, og den kan eftergøres ved procedurer, som fremmer frigørelsen af endogen gastrin. I dyreeksperimentelle undersøgelser følges injektion af gastrin antiserum af et gradvist fald i sphinctertrykket. Disse karakteristika tillader at konkludere, at serum gastrin er en faktor af betydning i den fysiologiske regulation af sphinctertrykket og en væsentlig faktor for opretholdelse af det normale tryk.

Injektion af sekretin, i doser som er mindre end den dosis der er nødvendig for en maksimal effekt på den exokrine sekretion fra pankreas, er uden effekt på det basale sphinctertryk, men hæmmer den gastrin-stimulerede sphincter med en kompetitiv kinetik. Denne effekt kan eftergøres ved installation af saltsyre i duodenum. Det må derfor accepteres, at serum sekretin er medvirkende i den fysiologiske regulation af sphinctertrykket.

Der er desuden foretaget undersøgelser over effekten af glucagon og cholecystokinin på sphinctertrykket, men resultaterne tillader ikke at konkludere vedrørende disse hormoners funktion i den fysiologiske regulation af sphinctertrykket.

KAPITEL IV

Dette kapitel indledes med en gennemgang af det apparatur og den fremgangsmåde, som er anvendt i det foreliggende arbejde. Herefter omtales og illustreres de forskellige karakteristika ved de normale og de abnorme kurvetyper. Der foretages endvidere en gennemgang af de kriterier, hvorefter patientmaterialet er udvalgt, og der afsluttes med en karakteristik af de forskellige parametre i normalmaterialet og undersøgelser vedrørende reproduktion af det gastro-oesophageale sphinctertryk.

Diskussionen koncentrerer om tre emner, – tekniske problemer ved trykregistrering i den gastro-oesophageale sphincter og i corpus oesophagei, en sammenligning mellem det foreliggende og tidligere offentliggjorte normalmaterialer og betydningen af de forskellige abnormiteter i kurvemønstret.

Det konkluderes, at det apparatur og den fremgangsmåde som er anvendt i det foreliggende arbejde tillader en pålidelig registrering af trykket i fundus, trykket i den gastro-oesophageale sphincter, relaxationen i sphincteren og det basale tryk i corpus oesophagei. Da systemet ikke kan registrere hurtige trykvariationer, er det uegnet til registrering af varigheden af sphincterens relaxation og de trykændringer som induceres i corpus oesophagei ved synkning. Det konkluderes endvidere, at de indbyrdes forskelle i de offentliggjorte normalmaterialer kan henføres til forskelle i udvælgelsen af materialet, i den fremgangsmåde som anvendes ved aflæsning af kurverne, i tryksondens konstruktion og i undersøgelsens udførelse. Det må fortsat betragtes som uafklaret, om de forskellige abnormiteter i kurvemønstret, "double peak of pressure" og "double respiratory reversal", kan forekomme ved normale anatomiske forhold, eller om de er betinget af afvigelser fra den normale anatomi i den gastro-oesophageale region.

KAPITEL V

I et materiale på 98 patienter med dyspepsi uden påviselig organisk årsag fordeler sphinctertrykkene sig både indenfor og udenfor normalområdet. I 54 tilfælde var det af samme størrelsesorden som hos normale, i 17 var det lavere end og i 27 højere end henholdsvis den nedre og den øvre grænse for normalområdet.

Det gennemsnitlige tryk hos patienter med pyrosis er lavere end hos normale. Der er imidlertid en betydelig overlapning mellem de to fordelinger.

Det gennemsnitlige sphinctertryk hos 23 patienter med periodisk dysphagia er højere end hos normale. Sammenlignet med patienter uden dysphagia, har patienter med dysphagia en hyppigere forekomst af abnormiteter i relaxationen i sphincteren og i motiliteten i corpus oesophagei.

Diskussionen er opdelt i tre afsnit, og i det første diskuteres patogenesen ved pyrosis, relationen mellem sphinctertrykket og reflux og de patofysiolo-

giske mekanismer ved et lavt tryk. Det konkluderes, at en kortvarig registrering af sphinctertrykket ikke kan anvendes til at belyse om et sygdomsbillede, helt eller delvis, kan henføres til reflux. Hvad angår et lavt tryk kan det formodes, at et lavt serum gastrin kan være årsagen i nogle tilfælde, men der foreligger intet direkte bevis herfor.

I det andet afsnit omtales det kliniske billede ved den hypertensive sphincter. Det fremhæves, at den hypertensive sphincter i nogle tilfælde må accepteres som en selvstændig symptomgivende sygdomsenhed.

I det tredje afsnit omtales relationen mellem tilstedeværelsen af dysphagia og forekomsten af abnormiteter i relaxationen i sphincteren og i motiliteten i corpus oesophagei.

KAPITEL VI

Der foretages en gennemgang af det kliniske billede og de manometriske resultater hos 73 patienter med hiatushernie af glidetype. I 34 tilfælde var trykket lavere end den nedre grænse for normalområdet, i 28 var trykket indenfor normalområdet og i 11 tilfælde var sphincteren hypertensiv. Patienter med pyrosis eller smerter og pyrosis havde et gennemsnitligt sphinctertryk, som er lavere end hos normale. Det samme var tilfældet for gruppen af patienter med pyrosis og dysphagia eller smerter, pyrosis og dysphagia. Der er imidlertid en betydelig overlapning mellem disse to fordelinger og normale. Patienter med dysphagia eller smerter og dysphagia havde et gennemsnitligt tryk, som ikke er forskellig fra det normale gennemsnit.

Resultaterne sammenlignes med tidligere offentliggjorte og analyseres i relation til undersøgelser, som har behandlet problemet vedrørende sphincterfunktionen i afhængighed af beliggenheden.

Det konkluderes, at den manometriske undersøgelse er en væsentlig supplerende undersøgelse ved hiatushernie. I tilfælde med et lavt tryk må resultaterne betragtes som vejledende, og en nærmere afklaring af sammenhængen mellem reflux og symptomer kræver supplerende diagnostiske undersøgelser. I tilfælde med hypertensiv sphincter eller spastisk oesophagus er den manometriske undersøgelse den diagnostisk afgørende.

KAPITEL VII

I dette kapitel præsenteres resultaterne fra en undersøgelse af det gastrooesophageale sphinctertryk i et materiale bestående af 56 patienter med ulcus duodeni, 12 med ulcus præpyloricum og 14 med ulcus ventriculi. Hos patienter med ulcus duodeni er det gennemsnitlige tryk lavere end hos normale. I de to øvrige grupper er det gennemsnitlige tryk af samme størrelsesorden som hos normale. I tilfælde med ulcus duodeni er det gennemsnitlige

sphinctertryk lavere hos patienter med pyrosis end hos patienter uden pyrosis. Det er ikke muligt, hverken ved ulcus duodeni, ulcus præpyloricum eller ved ulcus ventriculi, at påvise en sammenhæng mellem sphinctertrykket og henholdsvis den basale og den stimulerede syresekretion.

Diskussionen koncentrerer sig om de patofysiologiske mekanismer bag det lave tryk ved ulcus duodeni. Der foretages en gennemgang af tre mulige årsager, – ændringer i serum gastrin, – ændringer i det intragastriske milieu og – direkte hæmmende impulser via nervus vagus.

Det konkluderes, at det er usandsynligt, at et lavt serum gastrin kan være årsagen. Det er heller ikke muligt at fremføre holdepunkter for, at en forøgelse af den basale syresekretion reflektorisk kan reducere sphinctertrykket. Den mest sandsynlige forklaring er, at direkte hæmmende impulser, via nervus vagus, er et led i det patofysiologiske kompleks ved ulcus duodeni.

KAPITEL VIII

Dette kapitel omhandler resultaterne fra en undersøgelse af det gastro-oesophageale sphinctertryk hos patienter efter forskellige typer af ventrikelkirurgi. Det gennemsnitlige tryk efter komplet, trunkal vagotomi og pyloroplastik er af samme størrelsesorden som hos normale. Det gennemsnitlige tryk efter komplet, trunkal vagotomi og distal resektion er lavere end det gennemsnitlige tryk hos såvel patienter efter komplet, trunkal vagotomi og pyloroplastik som normale. Efter distal resektion uden vagotomi havde patienter i velbefindende et gennemsnitligt tryk som er lavere end hos normale. Patienter med sequelæ af ukendt oprindelse havde et gennemsnitligt tryk, som er højere end det gennemsnitlige tryk hos såvel normal som patienter i velbefindende efter den samme operation.

Hos 22 patienter, som fik foretaget distal resektion uden vagotomi, er det gennemsnitlige postoperative tryk ikke forskelligt fra det præoperative.

Diskussionen koncentrerer sig om disse resultater i relation til den nuværende viden om den neurogene og hormonale regulation af sphinctertrykket. I tilslutning hertil foretages en gennemgang af receptorer i ventriklen og nervus vagus' funktion som afferent ledningsbane for reflekser fra ventriklen til den gastrooesophageale sphincter.

Det konkluderes, at resultaterne hos patienter efter vagotomi og pyloroplastik, og efter vagotomi og resektion, er i overensstemmelse med den nuværende opfattelse af relationen mellem serum gastrin og sphinctertrykket. Det høje tryk hos patienter med sequelæ efter resektion uden vagotomi kan ikke forklares ud fra operativt inducerede ændringer i serum gastrin. Den mest sandsynlige forklaring er, at det høje tryk er resultatet af en reflektorisk meddelt tensionsforøgelse i den gastrooesophageale sphincter.

KAPITEL IX

I dette kapitel præsenteres resultaterne fra en undersøgelse af det gastro-oesophageale sphinctertryk hos patienter med sygdomme i galdevejene og resultaterne fra en undersøgelse over effekten af kolecystektomi på sphinctertrykket.

I et materiale på 121 tilfælde af operativt verificerede galdesten er det gennemsnitlige sphinctertryk ikke forskellig fra det normale. Der var imidlertid 16 med tryk, som er lavere end den nedre grænse for normalområdet og 28 med et tryk, som er højere end den øvre grænse for normalområdet.

I en gruppe på 74 patienter med operativt verificerede galdesten er det gennemsnitlige præoperative sphinctertryk ikke forskellig fra det postoperative gennemsnit.

I et materiale på 35 patienter med postkolecystektomisyndrom uden hiatus-hernie er det gennemsnitlige sphinctertryk højere end hos normale.

Diskussionen er opdelt i to afsnit, og koncentrerer om de mulige årsager til de registrerede afvigelser fra det normale sphinctertryk. Det første afsnit omhandler reflektorisk udløste ændringer i sphinctertrykket, og i relation hertil foretages en gennemgang af det anatomiske og fysiologiske grundlag for afferent refleksaktivitet fra galdevejene til den gastro-oesophageale sphincter og ventriklen. I det andet afsnit omtales undersøgelser vedrørende patofysiologiske forhold i galdevejene som årsag til ændringer i serum gastrin.

Det konkluderes, at det, med støtte i tidligere offentliggjorte undersøgelser, er muligt at fremføre holdepunkter for såvel reflektorisk som hormonal udløste ændringer i sphinctertrykket ved patofysiologiske forhold i galdevejene. En nærmere afklaring vil imidlertid kræve anvendelse af et dignostisk apparatur, som er større end det, der er anvendt i det foreliggende arbejde.

Det konkluderes endvidere, at den hypertensive sphincter kan forekomme hos individer, som tidligere har fået foretaget kolecystektomi, men som på undersøgelsestidspunktet er uden symptomer fra øvre abdomen. Det må derfor accepteres, at den hypertensive sphincter i nogle tilfælde kan forekomme uden ledsagende symptomer.

KAPITEL X

I dette kapitel er der foretaget en gennemgang af resultaterne af selektiv resektion af ramus hepaticus som behandling i udvalgte tilfælde af hypertensiv gastro-oesophageal sphincter. Materialet er på syv patienter, seks med postkolecystektomisyndrom og een med dyspepsi. Selektiv resektion af ramus hepaticus resulterede i et fald i sphinctertrykket i alle tilfælde, og et fald i det gennemsnitlige sphinctertryk fra 34 til 11 mm Hg. Operationen var uden effekt på det intraoperative tryk i choledochus. Der er ingen korrelation mel-

lem faldet i sphinctertrykket og de intraoperative ændringer i trykket i choledochus.

Det kliniske resultat var dårligt. To patienter angav, at operationen var uden effekt på symptomerne, og i de resterende fem tilfælde var der postoperativt symptomer af samme type som præoperativt, men mindre intense.

Det konkluderes, at den hypertensive gastro-oesophageale sphincter, i det foreliggende materiale, var uden relation til, eller kun delvis ansvarlig for, de præoperative symptomer.

KAPITEL XI

Der foretages en sammenfattende gennemgang af de konklusioner, som kan udledes af resultaterne fra de forskellige undergrupper af det totale materiale.

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